

# Chlorinated Hydrocarbon Insecticides

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## 15.1 CLASSIFICATION OF CHLORINATED HYDROCARBON INSECTICIDES

All chlorinated hydrocarbon insecticides are aryl, carbocyclic, or heterocyclic compounds of molecular weights ranging from about 291 to 545. Their cyclic structure and their greater molecular weight set them apart chemically from the chlorinated hydrocarbons used as solvents and fumigants (molecular weight < 236), which are described in Chapter 14. In a biological context the chlorinated hydrocarbon insecticides also differ from the chlorinated hydrocarbon solvents in that the former are generally stimulants of the nervous system while the latter are depressants. However, this distinction is not absolute: the  $\gamma$  isomer of benzene hexachloride ( $\gamma$ -BHC; lindane) is a stimulant, but two other isomers have an opposite effect.

The chlorinated hydrocarbon insecticides may be divided into five groups: DDT and its analogs, BHC, cyclodienes and similar compounds, toxaphene and related chemicals, and the caged structures mirex and chlordane. There is a greater tendency of insects to develop overlapping resistance to insecticides within each group than between groups, the latter probably reflecting differences in modes of action. However, overlapping of resistance between groups does occur.

In spite of some similarity of chemical structure and pharmacological effect, the individual insecticides within each group differ widely in toxicity and in their capacity for storage. Furthermore, toxicity and storage do not always vary in a parallel way. Methoxychlor is much less toxic and much less stored than DDT, whereas endrin, which is more toxic than dieldrin, is stored far less. Thus, each compound must be judged separately.

Although the organochlorine insecticides were widely used in agriculture and malarial control programs from the 1940s to 1960s with dramatic beneficial effects, they have come into disfavor because of their persistence in the environment, wildlife, and humans. The relatively low cost of these insecticides and unavailability of complete substitutes for some uses, how-

ever, ensure their continued use in many countries for some years to come.

The structures of the different chlorinated hydrocarbon insecticides are shown in the appropriate sections: DDT and analogs in Section 15.3, BHC in Section 15.4, cyclodienes in Section 15.5, toxaphene in Section 15.6, and mirex and chlordane in Section 15.7.

## 15.2 TOXICOLOGY OVERVIEW

### 15.2.1 SYMPTOMATOLOGY

In general, the signs of poisoning produced by different chlorinated hydrocarbon insecticides are similar, that is, expressions of neuronal hyperactivity. However, there are certain differences between the effects of DDT and its analogs, on the one hand, and all other chlorinated hydrocarbon insecticides on the other. Not only is tremor characteristic of poisoning by DDT, but also the onset of poisoning by it occurs with easily detectable mild effects that progress gradually, but continuously, to the point of convulsions. In contrast, lindane, aldrin, dieldrin, endrin, toxaphene, and several related compounds frequently produce illness in which a convulsion is the first sign of injury. This is true not only in experimental animals but also in people, who sometimes report that they experienced no prodromal symptoms of any kind prior to the initial fit. As described under Effects on the Nervous System in Section 15.3.1.2, with rats the incoordination associated with tremor induced by DDT may be demonstrated by measuring how long they can stay afloat in cool water. Whereas DDT causes marked reduction in swimming time at dose levels that cause no other clinical effect, dieldrin and some other pesticides interfere with swimming only at dosages that depress food intake and reduce weight gain so that it is reasonable to assume that the animals are weak. Thus it is probable that the incoordination observed in animals and people poisoned by these insecticides, other than DDT and its analogs, is different from



the tremor caused by DDT and should be referred to as ataxia or some other term.

The degree of stimulation of the nervous system appears to be related directly to the concentration of these insecticides in nerve tissue at the time. Usually the effect is rapidly reversible in animals after either single or multiple doses. Recovery occurs when the concentration of the chlorinated hydrocarbon insecticide in the nervous system falls below a critical level. It should be noted that this does not necessarily imply a loss of the chemical from the body but rather a redistribution to other tissues, such as adipose tissue, and has been studied particularly in connection with dieldrin (see Section 15.5.4.2).

## 15.2.2 ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

### 15.2.2.1 Routes of Absorption

All chlorinated hydrocarbon insecticides can be absorbed through the skin as well as by the respiratory and oral routes. The importance of dermal absorption varies greatly for the different compounds. This is partly because some of them, such as methoxychlor, have such a low toxicity that a small amount absorbed by any route is of no importance; more importantly, the efficiency of dermal absorption varies for the different insecticides. For example, DDT is poorly absorbed by the skin from solutions, and the absorption of solid material is so poor that it is difficult or impossible to measure either the uptake of DDT or its effect. In contrast, even solid dieldrin, if very finely ground, is absorbed so effectively through the skin that it is about half as toxic when applied dermally as when administered by mouth. The dermal penetration of these insecticides involves not only partition coefficients but also binding to various dermal, epidermal, and serum sites. This leads to complications in interpreting experimental findings from a kinetic viewpoint (Shah *et al.*, 1981).

Because of their relatively low vapor pressure, chlorinated hydrocarbon insecticides seldom reach levels in the air above those permitted. Of course, they may be absorbed from the lung if they reach the respiratory epithelium in the form of solid or liquid aerosols of appropriate particle size.

The intestinal absorption of lipophilic substances such as these insecticides will be influenced by fiber and fat constituents of the diet as well as by the total food intake. The absorption of dieldrin, for instance, is enhanced by starvation (Heath and Vandekar, 1964).

### 15.2.2.2 Distribution, Metabolism, and Excretion

Chlorinated hydrocarbon insecticides have become infamous because of their tendency to accumulate in humans, animals, birds, and the general environment. After single or repeated doses, most of these chemicals eventually reach their highest concentrations in adipose tissue with somewhat lower levels in other tissues with high contents of neutral lipids, such as adre-

nals. Although storage in adipose tissue can be partly explained by the lipophilicity of these insecticides, other factors such as structural elements of the chemical and competition between binding sites in lean and adipose tissue are of great importance (Bickel, 1984). Another, perhaps even more important factor is the rate of metabolism and excretion of the parent chemical and any metabolites. For instance, DDT and its primary metabolite DDE are stored in adipose tissue of humans, whereas the closely related insecticide methoxychlor, which is metabolized much more rapidly, occurs in fat only at very low levels. Indeed, this difference has led to the increasing use of methoxychlor as an insecticide with the decline in the popularity of DDT. The isomers of BHC are stored to very different degrees in a pattern that does not correspond to their solubility in body fat (see Section 15.4.1.2) and is probably due to some extent to differential metabolism. Dieldrin is stored avidly, whereas its isomer endrin is stored so little that it has been detected in patients only after acute exposure and not even in people engaged in its manufacture (see Section 15.5.5.3). Again, this is due to differential metabolism; the unhindered *anti*-C-12 hydrogen in endrin makes this position far more susceptible to attack than any other position in either isomer (Bedford and Hutson, 1976). Metabolites of dieldrin are thus excreted at a much lower rate in bile and feces than are those from an equal dose of endrin (Cole *et al.*, 1970). Of course, in itself, storage of chemicals in adipose tissue can be viewed as a detoxification mechanism.

The specific metabolic transformations undergone by chlorinated hydrocarbon insecticides are covered in the appropriate sections. General principles of these metabolic routes are discussed in Chapter 3. In common with other lipophilic xenobiotics, chlorinated hydrocarbon insecticides can be metabolized by the microsomal cytochrome P-450 system to hydroxyl derivatives, perhaps with dehydrochlorination as observed for lindane, or by conversion to stable epoxides as in the case of the formation of dieldrin from endrin. The *O*-dealkylation of methoxychlor probably also involves a cytochrome P-450-mediated hydroxylation step. Other routes of metabolism involve conjugation with glutathione to give eventually mercapturates which are usually excreted in the urine (see Section 15.4.1 for lindane), or the production of glucuronides, as in the case of the alcohol formed by reduction of chlordecone (see Section 15.7.2).

Parent insecticides are usually excreted either in the bile or possibly through the intestinal wall. Both routes may be manifested ultimately as fecal excretion. Metabolites of the chlorinated hydrocarbon insecticides can also be excreted in the urine if they are of relatively high polarity. This may have involved resorption of conjugates from the intestinal tract and transport to the liver and kidney (enterohepatic circulation) followed by further metabolic transformations. Such would be the case for glutathione conjugates excreted in bile, some of which may be reabsorbed and converted to the mercapturates for urinary excretion.

An important consideration when discussing the excretion of chlorinated hydrocarbon insecticides is their presence



milk (Jensen, 1983). The lipid content of milk (3–5%) and high blood flow to breast tissue can lead to considerable concentration of these chemicals compared to that in tissues. Thus, contamination of both cow's milk and human milk is not just a form of excretion but a unique one that could also lead to toxic effects in the recipient. Infants in countries with a large use of insecticides could be at particular risk, especially since breast feeding is recommended by the World Health Organization and other health agencies. Levels of these chemicals in human milk can be 10 times those in cow's milk. Measurement of chlorinated hydrocarbon insecticides in human milk is a convenient method for determining exposure of populations to these compounds, although it is prone to variability due to the effects of age, smoking, diet, and other factors (Jensen, 1983).

The excretion of DDT, DDE, and dieldrin in association with hair has been reported (Matthews *et al.*, 1976), probably representing their presence in hair or skin oils.

### 15.2.2.3 Factors Influencing Storage and Toxicity

Although the interaction of pesticides among themselves or with other chemicals is outlined in Chapter 2, it is pertinent here to discuss the interaction between chlorinated hydrocarbon insecticides. The ways in which these compounds influence the metabolism of themselves or of others of the same group is complex and still poorly understood. The results are essentially opposite in some species compared to others.

In dogs, when dieldrin and DDT are administered together, the storage of dieldrin is decreased but that of DDT is *increased* compared to the storage when each insecticide is given separately (Deichmann *et al.*, 1971a). If both aldrin and DDT are fed simultaneously to dogs, the storage of both compounds is increased such that the storage of aldrin is about the same, and the storage of DDT, and especially DDE, is somewhat greater than when each compound is given alone but at twice the dietary concentration (Deichmann *et al.*, 1969).

In the trout the situation is similar to that in dogs (Mayer *et al.*, 1970; Macek *et al.*, 1970), and in trout methoxychlor behaves like DDT when combined with other compounds (Mayer *et al.*, 1970).

In Japanese quail, the storage of DDE is increased in the presence of dieldrin but the latter remains essentially unchanged (Ludke, 1974).

In rats, when the compounds are combined, the storage of dieldrin is markedly decreased while the storage of DDT is uninfluenced (Street, 1964; Street and Chadwick, 1967; Street and Blau, 1966; Pearl and Kupfer, 1972; Street *et al.*, 1966a,b). The actions of methoxychlor and hexachlorobenzene (Avrahami and Gernert, 1972) are similar to that of DDT in reducing dieldrin storage. Hexachlorobenzene (*not* BHC) will also reduce storage of aldrin but increase the storage of DDT and mirex (Clark *et al.*, 1981). At the same time, polar urinary metabolites of the insecticides are increased from aldrin and mirex but remain unchanged from DDT. Storage of heptachlor in rats is depressed by DDT (Street *et al.*, 1966b) and excretion

of [ $^{14}\text{C}$ ]dieldrin administered ip is stimulated (Pearl and Kupfer, 1972).

In guinea pigs, when DDT and dieldrin are fed together, the storage of dieldrin is little affected but that of DDT is decreased (Wagstaff and Street, 1971b).

Undoubtedly, the interaction of compounds of this type in different species depends in part on their ability to induce the microsomal drug-metabolizing enzymes in those species. However, relationships between induction, storage, and excretion of metabolites are rarely simple and there are few studies of the induction of the metabolism of one pesticide by another. Lindane and DDT have been found to be only moderately active inducers in guinea pigs although their storage is low, whereas dieldrin was a strong inducer, yet its storage is much higher than that of the other two insecticides (Wagstaff and Street, 1971b). In mice, treatment for 5 months with DDE decreased the urinary excretion of [ $^{14}\text{C}$ ]DDE and increased hepatic levels (Gold and Brunk, 1986). However, there was no effect on the levels of the only metabolite detected, 1,1-dichloro - 2 - (4-chlorophenyl) - 2 -- (3-hydroxy-4-chlorophenyl) ethane. It is very difficult to interpret experimental findings of this type in the context of human exposures both of the general population and of heavily exposed workers. Dose levels and routes of administration in experimental animals are usually much different from those experienced by humans. Thus there are few studies of the effects of these pesticides on their own metabolism or that of other insecticides in humans. One possible example is the finding that current and former endrin workers stored significantly lower levels of *p,p'*-DDE; in fact, the levels were below detectable limits (Jager, 1970).

Other xenobiotics and drugs will undoubtedly affect the storage, distribution, and metabolism of chlorinated hydrocarbon insecticides as described above for hexachlorobenzene. Recent progress in our understanding of the induction of the drug-metabolizing systems (e.g., cytochrome P-450 and glutathione transferase isoenzymes) in both animals and humans and the influence of age, sex, and genetics, however, should make interactions easier to predict.

The combined effect of chlorinated hydrocarbon insecticides and anticholinesterase insecticides is one form of interaction that has received special attention even though there is no evidence that it has ever been of any clinical importance. Pretreatment of experimental animals with various chlorinated insecticides (including aldrin, dieldrin, chlordane, and DDT) has afforded some protection against single doses of some anticholinesterases (Triolo and Coon, 1966a,b; Williams and Casterline, 1970; Deichmann and Keplinger, 1970; Bass *et al.*, 1972). In other instances, the toxicity of an organophosphorus insecticide is increased by pretreatment with chlorinated hydrocarbon insecticides. For example, the toxicity of fenitrothion in rats is increased by heptachlor (Mestitzová *et al.*, 1970a,b, 1971). In one case, protection by aldrin against parathion appeared after 16 hr, reached a maximum in 4 days, and lasted at least 12 days. A dose of 1 mg/kg provided significant protection (Triolo and Coon, 1966a,b). Most of these enhancing or protective effects of chlorinated hydrocarbon



insecticides are probably the consequence of induction of particular routes of metabolism and should now be mostly predictable. Piperonyl butoxide, an inhibitor of cytochrome P-450, will block the protective action of chlorinated insecticides on 6-chloro-3-xylyl methylcarbamate (Williams and Casterline, 1970). Chlorinated hydrocarbon insecticides appear to have an affinity for a hydrophobic site of cholinesterase although they do not inhibit the active site of the enzyme (Mayer and Himel, 1972); whether this interferes with the approach of the substrate to the active site is not known.

Mobilization of fat in adipose tissue due to starvation or other reasons can release into the circulation stored chlorinated hydrocarbon insecticides, sometimes with marked effects.

### 15.2.3 MODES OF ACTION AND CAUSE OF DEATH

#### 15.2.3.1 Effects on the Central Nervous System

**Mode of Action** As discussed elsewhere (Section 4.1.2.3), there is considerable evidence to suggest that the chlorinated hydrocarbon insecticides act by altering the electrophysiological and associated enzymatic properties of nerve cell membranes, causing a change in the kinetics of  $\text{Na}^+$  and  $\text{K}^+$  ion flow through the membrane. Disturbances of calcium transport or  $\text{Ca}^{2+}$ -ATPase activity may also be involved, as well as phosphokinase activities (Matsumura and Patil, 1969; End *et al.*, 1981; Joy, 1982a; Shankland, 1982; Tilson and Mactutus, 1982; Woolley *et al.*, 1985; Ishikawa *et al.*, 1989). Other cell membranes may also be affected by related mechanisms. Dieldrin at a concentration of  $10 \mu\text{M}$  affects liver cell membranes in a way very similar to that of the insect nervous system *in vivo* (Wang and Matsumura, 1969). DDT and some of its analogs (but not others) have been shown to inhibit  $\text{Ca}^{2+}$ -ATPase from human term placentas (Treinen and Kulkarni, 1986). Most studies have been conducted with DDT (Section 15.3.1.2) and chlorodecone and other cyclodienes (Section 15.7.2.2). Full explanations for the differences in the *in vivo* neurotoxic effects of these two groups of chlorinated hydrocarbon insecticides are still not completely apparent, including the peripheral versus central nervous system (CNS) actions. DDT and its analogs appear to act particularly at the nerve axon by prolonging opening of the ion gates of the sodium channel (Ishikawa *et al.*, 1989), whereas cyclodienes, mirex, and lindane seem to act at presynaptic terminals. Lindane, toxaphene, and cyclodienes have been shown to inhibit *t*-butylbicyclopophosphorothionate binding to brain specific sites, indicating action at the  $\gamma$ -aminobutyric acid (GABA)-regulated chloride channel (Casida and Lawrence, 1985; Cole and Casida, 1986). DDT, mirex, and chlordecone had no effect. Cyclodienes and lindane also inhibit GABA-induced  $^{36}\text{Cl}$  influx into rat brain membrane microsacs (Abalis *et al.*, 1986).

Whatever the exact mechanisms, nonconvulsant doses of chlorinated hydrocarbon insecticides increase the susceptibility of animals to convulsions precipitated by many other poisons or by electroshock. One study of this relationship concluded

that the convulsant effects of dieldrin may be mediated by effects on the hippocampus and other limbic structures (Swanson and Woolley, 1978). Fonseca *et al.* (1986) have demonstrated that *p,p'*-DDT and lindane decrease the number of muscarinic receptor sites in selective regions of rat brain.

A toxic dosage of dieldrin (50 mg/kg) led to a decrease in norepinephrine in the brain of rats 5 hr after ingestion but no change in dopamine or serotonin. When rats were maintained on a dietary level of 80 ppm (about 2.4 mg/kg/day) that they tolerated well for more than 10 weeks, norepinephrine and serotonin (but not dopamine) were depleted in certain parts of the brain soon after feeding but later returned to normal values (Wagner and Greene, 1974). A decrease in brain stem norepinephrine and acetylcholine and an increase in serotonin have been observed in rats following toxic doses of several cyclodiene insecticides (Hrdina *et al.*, 1974). Similar changes were seen with DDT (Hrdina *et al.*, 1973). It is clear that changes in the biogenic amines parallel the toxicity of chlorinated hydrocarbon insecticides, including the phenomenon of initial illness followed by clinical recovery. Whether these changes in the biogenic amines are a cause or a consequence is not clear. What is certain is that a variety of stimuli, including electrical stimuli and some insecticides, can change the production of biogenic amines in the brain (Campos and Jurupé, 1970).

The relative acute toxicities of the chlorinated hydrocarbon insecticides in animals and humans have been listed by Joy (1982a). The cyclodienes endrin, dieldrin, and isobenzan appear to be among the most toxic to humans and perhaps >10-fold more acutely toxic than DDT, which is the most potent agent in the dichlorodiphenylethane group.

**Origin of Fever** Fever may be a specific result of poisoning of the temperature control center in the brain. The effect may be more common than has been recognized. What has been recognized in a few human cases is high fever of sometimes late but sudden onset, frequently followed promptly by death. This kind of fever has been observed in poisoning by BHC, dieldrin, and endrin.

Fortunately, high fever of central origin is rare, but because it is such a grave sign, it is essential to distinguish it from other kinds of fever that may be the result of poisoning. Fever may accompany convulsions in humans or larger animals simply because it may be impossible to dissipate heat as rapidly as it is generated by the violent activity, which certainly is muscular and may be metabolic also. Fever of this origin has no special prognostic significance beyond that of the convulsions that give rise to it.

Regardless of the exact cause, a moderate increase in body temperature during the early course of illness carries no serious implications (Osuntokun, 1964). However, unless fever subsides promptly after convulsions are controlled, some other basis for it must be sought.

Fever may also be a response to chemical pneumonitis following aspiration of solvents or other chemical irritants; of course, fever of this origin may occur after a formulation of



any chlorinated hydrocarbon insecticide has been aspirated. It may depend in part on secondary infection. Usually it is delayed about 12 hr or more, and in relatively mild cases it may not appear until the patient has recovered from neurological manifestations.

**EEG** It is clear that the electroencephalogram (EEG) is a good index of the convulsive action of chlorinated hydrocarbon insecticides (Joy, 1982a). The sequence of EEG changes following a single convulsive dose of DDT and dieldrin to cats has been reported (Joy, 1973).

**Pathology** Chlorinated hydrocarbon insecticides produce little morphological change in the CNS of animals even when given in single or repeated doses sufficient to kill. The changes that do occur seem to reflect the agonal state but are not sufficient to account for death or assist in diagnosis, and they have been discussed by Joy (1982a).

### 15.2.3.2 Effects on the Liver

There is no doubt that DDT and a number of other chlorinated hydrocarbon insecticides cause marked changes in the livers of various rodents and that these changes progress to tumor formation in some species, especially the mouse. However, the relationship of these tumors arising in rodents to the potential induction of hepatocellular carcinoma in humans is still very obscure, as exemplified by DDT (Anderson, 1985), although the view that they are peculiar to rodents may not be completely justified, since for practical and financial reasons there have been few studies with other species.

Evidence for the carcinogenicity of chlorinated hydrocarbon insecticides has been reviewed by the International Agency for Research on Cancer (IARC) on a number of occasions during the last two decades. The IARC evaluation of these chemicals when administered by the oral route is shown in Table 15.1. Most of the insecticides produce tumors in mice, but results in rats are less conclusive. None of the chemicals have been completely negative in both rats and mice. Perhaps for this reason and the fact that their mechanism of action in liver has not yet been completely elucidated, the IARC seem reluctant to state categorically that they pose no carcinogenic risk to humans.

In connection with DDT, which has been studied the most in this group of chemicals, it has been concluded that the evidence for carcinogenicity in humans is inadequate (IARC, 1982, 1987). In mice the oral hepatocarcinogenicity has been demonstrated in several strains and shows a dose-response relationship. A dietary level of 2 ppm (about 0.3 mg DDT/kg/day) produces a significant increase of hepatomas in male but not female CF1 mice and not in either sex of BALB/c mice. Increased tumor incidence (particularly lung adenomas) has also been reported in some other organs of mice. There is now clear evidence, confirming the preliminary studies of Fitzhugh and Nelson (1947), that DDT can be hepatocarcinogenic to rats (Rossi *et al.*, 1977; Cabral *et al.*, 1982b). Results in hamsters,

**Table 15.1**

Summary of the Oral Hepatocarcinogenicity of Some Chlorinated Hydrocarbon Insecticides in Animals as Assessed by IARC Working Groups on the Evaluation of Carcinogenic Risk of Chemicals to Humans (1974, 1979, 1982, 1983, 1987)<sup>a</sup>

| Chemical        | Species | Evaluation  |
|-----------------|---------|---|
| DDT             | mouse   | positive in both sexes and in various strains   |
|                 | rat     | positive  |
|                 | hamster | negative  |
|                 | dog     | inconclusive  |
|                 | monkey  | inconclusive  |
| DDE             | mouse   | positive  |
| methoxychlor    | mouse   | positive  |
|                 | rat     | inconclusive  |
| chlorobenzilate | mouse   | positive  |
|                 | rat     | inconclusive  |
| dicofol         | mouse   | positive in males   |
|                 | rat     | inconclusive  |
| BHC             | mouse   | technical mixture, $\alpha$ isomer and $\gamma$ isomer (lindane) positive; $\beta$ isomer limited positive evidence |
|                 | rat     | inconclusive  |
| chlordane       | mouse   | positive  |
|                 | rat     | inconclusive  |
| heptachlor      | mouse   | positive  |
|                 | rat     | inconclusive  |
| aldrin          | mouse   | positive  |
|                 | rat     | negative or inconclusive  |
| dieldrin        | mouse   | positive  |
|                 | rat     | negative  |
|                 | dog     | inconclusive  |
|                 | monkey  | inconclusive  |
| endrin          | mouse   | inconclusive  |
|                 | rat     | negative or inconclusive  |
| toxaphene       | mouse   | positive  |
|                 | rat     | negative  |
| mirex           | mouse   | positive in two strains   |
|                 | rat     | positive  |
| chlordecone     | mouse   | positive  |
|                 | rat     | positive  |

<sup>a</sup> Evaluations for chlorobenzilate, methoxychlor, BHC, and toxaphene in rats may have to be revised; see Sections 15.3.4, 15.3.5, 15.4.1, and 15.6.1.

dogs, and monkeys appear to be still inconclusive, although hamsters do give liver tumors with *p,p'*-DDE, as do mice (Cabral, 1985). There appear to have been no new studies of the hepatocarcinogenicity of DDT in dogs and monkeys since those first reported (IARC, 1974). These studies, which were inconclusive, did continue for some time (monkeys up to 7.5 years), and though the numbers were small they were no less than those which had given positive results for other potential carcinogens.

Chlorinated hydrocarbon insecticides are, in general, negative in mutagenicity tests (Wildemaue *et al.*, 1983). Whether their tumorigenicity in rodents is due to the promotion of spontaneous initiated events is not known. It is clear, however, that DDT, BHC, and the cyclodiene insecticides are efficient promoters of the actions of recognized potent hepatocarcinogens such as diethylnitrosamine and 2-acetylaminofluorene (Peraino *et*



*al.*, 1975; Williams and Numoto, 1984; Schulte-Hermann, 1985). The ability of these chemicals to cause tumors in the liver and promote those initiated by other carcinogens is probably tied up with the induction of microsomal and other enzyme systems. The following paragraphs are concerned with these matters.

**Early Changes in the Rodent Liver Associated with Induction of Microsomal Enzymes** The response of the rodent liver to DDT is entirely similar to its response to moderate dosages of BHC, chlordane, dieldrin, toxaphene (Lehman, 1951, 1952; Ortega *et al.*, 1956), and the important drug phenobarbital (Stevenson and Walker, 1969; Wright *et al.*, 1972; Thorpe and Walker, 1973). Similar early changes also were demonstrated in the livers of rats fed dimethrin, pyrethrins, and especially synergized pyrethrins (Kimbrough *et al.*, 1968) (see Chapter 13). Some of these lesions are also known to arise spontaneously (Popp *et al.*, 1985).

The earliest changes in some liver cells of rodents administered DDT involve so much increase in the smooth endoplasmic reticulum of individual cells that they enlarge, and the large granules that ordinarily are scattered throughout the cytoplasm are displaced to the periphery of the affected cell. Quite early, some of the endoplasmic reticulum forms whorls that may have fat droplets as their centers—this justifying the term “lipospheres” applied to them by Ortega *et al.* (1956, 1957). Others have referred to these inclusions as “hyaline oxyphil masses” (Lillie and Smith, 1944), “lamellar bodies” (Ito *et al.*, 1973), or “myelin whorls” (Hansell and Ecobichon, 1975). These changes are accompanied by some increase in fat droplets, not all of which become surrounded by endoplasmic reticulum. This cluster of changes (hypertrophy, margination, and lipospheres) is characteristic of the response of rodents to compounds that induce microsomal enzymes. The characteristic changes develop promptly. An increase in smooth endoplasmic reticulum and the appearance of lamellar structures have been seen as early as 4 and 7 days after dosing began (Wright *et al.*, 1972). When DDT was administered to rat dams by stomach tube for 3 days at the rate of 50 mg/kg/day, no significant induction of liver microsomal enzymes and no morphological changes in the hepatocytes of the pups were observed prior to their birth, even though residues were found in fetal tissues. The young of treated mothers did show increased smooth endoplasmic reticulum, lipid inclusions, and myelin whorls when they were 4 days old and thereafter, and no samples were collected from birth until day 4. Similar but somewhat lesser changes were produced on the same schedule by phenobarbital (75 mg/kg/day) (Hansell and Ecobichon, 1975).

The accumulation of lipid following a single large dose of dieldrin was reported to involve triglycerides only, with no increase in phospholipid or cholesterol. The increase in triglycerides was accompanied by increased incorporation of [ $^{14}\text{C}$ ]glucose into glyceride-glycerol but a decrease of its incorporation into fatty acids (Bhatia and Venkatasubramanian,

1972). Presumably, more triglyceride is formed in the presence of more glyceride-glycerol.

Certain changes other than the characteristic one have been reported but not confirmed. These include enlargement and morphological change of the mitochondria (Obuchowska and Pawlowska-Tochman, 1973; Watari, 1973), increased numbers of primary lysosomes, and atrophy of the Golgi body (Watari, 1973), none of which were found by Ortega (1966).

Although microsomal enzymes may be induced in other species, their livers do not seem to show the same morphological changes as viewed by light microscopy (Laug *et al.*, 1950; Lehman, 1951, 1952; Ortega *et al.*, 1956; Stevenson and Walker, 1969) or show them to a lesser degree as viewed by electron microscopy (Wright *et al.*, 1972).

The changes in liver cells that characterize induction of microsomal enzymes in rodents are distinct from the focal necrosis that may be produced with about the same ease in the livers of rodents or of other species by fatal or near-fatal dosages of chlorinated hydrocarbon insecticides. These necrotic lesions have been described by Smith and Stohlman (1944), Lillie *et al.* (1947), Nelson *et al.* (1944), Cameron and Burgess (1945), Deichmann *et al.* (1950), and Ortega *et al.* (1956). The necrosis does not appear to progress, since if high dosages are continued the animals die, whereas if dosing is stopped and the animals survive, the necrotic cells are removed by autolysis and phagocytic action. The lesions then heal, usually without scarring (Cameron and Burgess, 1945), although this can occur (Lillie and Smith, 1944; Lillie *et al.*, 1947). An interesting indication of the defensive or adaptive nature of the characteristic liver changes is the observation that they occur only in animals that remain healthy and not in animals that are frankly intoxicated by very high dosage levels (Ferrigan *et al.*, 1965). This does not mean that rats that have developed the changes may not later show signs of poisoning.

On the other hand, there is one aspect of the morphological change in the endoplasmic reticulum that may be even more critical than marked hypertrophy of the smooth variety in determining whether tumorigenesis will occur. Williams and Rabin (1971) reported that a range of established carcinogens promoted the degranulation of rat liver rough endoplasmic reticulum *in vitro*, whereas a range of noncarcinogens were without this effect. In a parallel way, carcinogens prevented smooth microsomal membranes from binding added ribosomes in the presence of estradiol. Wright *et al.* (1977) showed that results of biochemical tests for degranulation corresponded not only to the tumorigenicity of different compounds but also to differences in the susceptibility of different species and strains and of males and females of the same strain.

**The Question of Reversibility and the Relation of Dosage to Induction of Microsomal Enzymes** At least in their early stages, the changes in liver cells that characterize induction of microsomal enzymes in rodents are reversible (Fitzhugh and Nelson, 1947; Ortega *et al.*, 1956; Wright *et al.*, 1972). The reversibility does not depend on cell removal but simply on



reversion of the physiological and morphological condition of the cells to their original condition. Return of the liver to normal size also occurs if dosage is discontinued soon enough (Kunz *et al.*, 1966). On the other hand, normalization may be slow, especially when the inducer remains in the target tissue. Although the liver weight of rats returned to normal within 2 weeks after one or two doses of  $\alpha$ -BHC at the rate of 200 mg/kg, the DNA content of the liver remained high, as did the proportion of the cells with tetraploid nuclei during a 7-week posttreatment period (Schulte-Hermann *et al.*, 1971). In rats fed photomirex (a degradation product of mirex) for 4 weeks (50 ppm), histological changes in the liver and thyroid could still be seen 48 weeks after return to normal diet (Chu *et al.*, 1981a,b). Consistent with these persistent changes was the finding of significant levels of photomirex remaining in the liver.

Of course, reversibility is incompatible with progression, but whether observed irreversibility will be associated with progression must be determined directly in each instance. In the following paragraphs, the question of progression is discussed only after consideration of the problem of irreversibility in general.

If dosing with chlorinated hydrocarbon insecticides or other inducers is continued long enough and at a sufficiently high level, the liver changes become irreversible, if for no other reason than that the remaining life span of the animals is too short to permit excretion of the inducing chemical or complete reversion of the liver cells to their original state. Just when this shift to irreversibility occurs remains unknown, but it seems very likely that dosages sufficient to produce irreversible morphological change also exceed the physiological adaptability of the liver. The important distinction between adaptation and injury as it relates to enzyme induction and liver morphology has been studied in relation to dieldrin (see Section 3.1.2.3). The matter has received some biochemical study, which suggested that hypoactive hypertrophic endoplasmic reticulum involves a qualitative change in the induced cytochrome P-450 (Stevens *et al.*, 1977).

Briefly, the evidence is strong that enlargement of the liver and of individual liver cells is adaptive at dosages where the increase in endoplasmic reticulum is accompanied by a parallel increase in activity of the associated enzymes and by no depression in the activity of other enzymes and that these liver changes are pathological at higher dosages where the activity of the drug-metabolizing enzymes fails to keep pace with the morphological changes or where the activities of these or other enzymes are depressed.

The relation of dosage to the induction of microsomal enzymes has been discussed previously (see Sections 2.3.8 and 7.4.3). The effects of DDT were explored by Kinoshita *et al.* (1966) and later studied more thoroughly by Hoffman *et al.* (1970). They found that, when DDT was fed to male weanling rats for only 14 days at dietary concentrations of 0.5–2048 ppm, concentrations of 0.5 and 2 ppm had no effect on the *O*-demethylation reaction used as a test, but concentrations of 4–750 ppm produced increases in the rate of metabolism propor-

tional to the log of dosage. Extrapolation of this portion of the dosage–response curve to the abscissa provided a calculated no-effect level of  $3.27 \pm 1.02$  ppm equivalent to about 0.327 mg/kg/day. This is in reasonable agreement with other estimates of the threshold for induction of various enzymes in the rat, including some studies involving longer administration of DDT. These estimates, expressed as milligrams per kilogram per day, are approximately 0.05 (Kinoshita *et al.*, 1966; Street *et al.*, 1969), 0.5 (Schwabe and Wendling, 1967), and 0.125 (Gillett, 1968). The relationship may not be the same for different inducers in the same species or for the same inducer in different species or sexes. For example, DDT in the squirrel monkey promotes the metabolism of EPN and *p*-nitroanisole; the first requires a DDT dosage of 5.0 mg/kg/day, but the latter requires only 0.5 mg/kg/day (Cranmer *et al.*, 1972). *In vivo* administration of both chlordecone and mirex induces the  $V_{\max}$  of *p*-nitroanisole metabolism by male rat microsomes and increases apparent  $K_m$  values, but with females this metabolism was reduced with either agent and the apparent  $K_m$  value was elevated by chlordecone but little affected by mirex (Ebel, 1984). Metabolism of DDT is promoted by DDT itself in the hamster (Gingell and Wallcave, 1974) but not in the mouse (Gingell and Wallcave, 1974) or in the squirrel monkey (Chadwick *et al.*, 1971b). However, most of the estimates for minimal effective dosage are of the same order of magnitude as 0.25 mg/kg/day, known to be effective in humans (Poland *et al.*, 1970), but all are more than 100 times greater than the highest dosage of people in the general population during the late 1960s (Duggan, 1968). In the study by Hoffman and his colleagues (1970), increase of the dietary level above 750 ppm produced no further increase in enzyme activity. Intake less than 128 ppm produced no increase in liver weight within the period of observation; increase was proportional to dosage within the range 128–512 ppm and was submaximal at intakes above 512 ppm.

The biochemical pattern of induction of mixed-function oxidase enzymes is similar for DDT and phenobarbital but distinctly different for 3-methylcholanthrene (Vainio, 1975). DDE, the major metabolite of DDT, was shown to induce mRNA for a cytochrome P-450 identical to that induced by phenobarbital but had a much more persistent effect (Morohashi *et al.*, 1984).

**Late Changes in the Rodent Liver Associated with Induction of Microsomal Enzymes** As indicated above, the earliest morphological changes caused by phenobarbital-type enzyme inducers in the rodent liver involve separate cells in the centrilobular area. If the dosage is sufficiently high and prolonged, nodules consisting entirely of hypertrophied cells may appear. At first, these microscopic nodules are distinguishable only by pattern; they have no bounding membrane and they do not compress or change in any other detectable way the smaller liver cells that surround them. Some nodules may become large enough to be seen without a microscope, and a few may exceed 1 cm in diameter. In these large nodules there is almost complete loss of lobular architecture. Nodules apparently were



first described by Fitzhugh and Nelson (1947), who felt they could be regarded as adenomas or as low-grade hepatic cell carcinomas. Just why this latter term was used is not clear because neither mitosis, tissue invasion, nor metastasis was observed. Although Ortega *et al.* (1956) reported small nodules in the livers of rats they had dosed and although they examined tissue loaned by Fitzhugh and Nelson's laboratory, they were entirely unimpressed by the lesions, referring to them as "focal incongruities."

The classification introduced by Thorpe and Walker (1973) and Walker *et al.* (1973) might have been expected to lead to better agreement or at least to a clearer definition of points of difference. As a result of their studies in mice, these investigators proposed that simple nodular growths of liver parenchymal cells be called type *a* lesions and that areas of papilliform and adenoid growth of tumor cells, sometimes accompanied by metastases to the lungs, be called type *b* lesions. It was concluded by Walker *et al.* (1973) on the basis of earlier studies of rats and dogs in their own laboratory and also on the basis of results of others that tumorigenic action of dieldrin had been demonstrated only in mice.

However, there still is no agreement regarding the carcinogenicity of the chlorinated hydrocarbon insecticides. The views of some pathologists remain diametrically opposite. This is true despite the finding of (a) pulmonary metastases of hepatic cells in mice that had received DDT (Tomatis *et al.*, 1972; Walker *et al.*, 1973),  $\beta$ -BHC,  $\gamma$ -BHC, dieldrin, or phenobarbital (Thorpe and Walker, 1973); or (b) progression of liver enlargement beginning 12 weeks after cessation of ingestion of  $\alpha$ -BHC by mice for 24 or 36 weeks (Nagasaki *et al.*, 1974) or progressive increase in the size of liver nodules after DDT feeding was stopped (Tomatis *et al.*, 1974b; Tomatis and Turusov, 1975); or even (c) in BHC-exposed mice the time pattern of increase in liver weight (as reflected in body weight), which gained momentum only after a delay of 4 weeks but showed a further acceleration in week 13 in spite of decreased food consumption (Tomii *et al.*, 1972), which appears to establish without question that at least some of the liver changes produced by these compounds in rodents are malignant.

Of course, the reasons for disagreement are that tumors indistinguishable from those caused by DDT, other chlorinated hydrocarbon insecticides, and phenobarbital occasionally occur in control mice (Davis and Fitzhugh, 1962; Walker *et al.*, 1973) and rats (Fitzhugh and Nelson, 1947; Popp *et al.*, 1985) and, more especially, because these tumors differ from real cancers in their biochemistry and they are not malignant in the classical sense. Specifically, (a) they do not actively invade tissues, (b) their "metastases" usually do not grow even through large growths of liver cells in the lungs occasionally have been seen (Walker *et al.*, 1973), (c) any shortening of life span that occurs may be related to the toxicity of large dosages and not to tumors *per se*, and finally (d) mice receiving DDT at a rate of 5.5 mg/kg/day as a result of dietary intake show a decrease in the success of transplantation and a significant increase in survival following inoculation with an otherwise

uniformly transplantable and uniformly fatal ependymoma (Laws, 1971).

Although the displacement of liver cells to the lung occasionally seen after prolonged dosage with DDT usually is referred to as metastasis, it might better be called embolism because the lesion rarely progresses and, therefore, usually lacks the clinical significance of real metastasis. Because it usually does not grow, the lesion is usually hard to find. A number of investigators have failed to mention liver cells in the spleen, lymph nodes, or lungs, and some have stated specifically that they were not found (Nagasaki, 1973).

Perhaps the most illuminating studies of the liver changes caused by various chlorinated hydrocarbon insecticides are those in which 2,7-fluorinediamine, diazoaminobenzene, or some other classical carcinogen has been used as a positive control (Wright *et al.*, 1972; Walker *et al.*, 1973; Kuwabara and Takayama, 1974). In each case the lesion caused by the classical carcinogen was different from that caused by the insecticide in one or more of the following ways: (a) it did not involve induction of microsomal enzymes; (b) it started as hyperplastic nodules rather than as isolated cell changes; (c) bile duct proliferation or other lesions not found in controls or in insecticide-treated animals were present; (d) the final lesion was hepatocellular carcinoma, in contrast to the adenoma caused by DDT or BHC; and (e)  $\alpha$ -fetoprotein was formed, which did not occur in connection with DDT or BHC. Other workers also have failed to find  $\alpha$ -fetoprotein in mice treated with a chlorinated hydrocarbon insecticide (Hanada *et al.*, 1973).

It must be emphasized that the chlorinated hydrocarbon insecticides and phenobarbital do not produce in other animals, to the same extent, the early, visible changes in the endoplasmic reticulum that are so characteristic of some rodents and that may progress to tumor formation in them. The fact that these compounds do not lead to tumor formation in other animals might have been predicted by the fact that they do not cause in other animals the early changes, characterized by hypertrophy, margination, and lipospheres. Of course, it must also be said that the number of studies that have been conducted with nonrodent species are relatively few. In addition, chlorinated hydrocarbon insecticides may all be positive carcinogens in the mouse but not all seem to cause tumors in rats (see Table 15.1) despite considerable induction of the endoplasmic reticulum by other chemicals in the group. On the other hand, large increases in liver size after lindane treatment in CF1 mice but not B6C3F1 mice or Osborne-Mendel rats do seem to correlate with propensities for tumor formation (Oesch *et al.*, 1982). In recent years, an epigenetic mechanism for the tumorigenicity of chlorinated hydrocarbon insecticides has become likely in which there is a disruption in intercellular communication—perhaps leading to inhibition of exchange of growth inhibitors (Maslansky and Williams, 1981; Tsushimoto *et al.*, 1983; Wärngård *et al.*, 1985, 1987, 1988, 1989, Zhong-Xiang *et al.*, 1986). How this would relate to induction of microsomal enzymes, if at all, is not yet clear.

The fact that chlorinated hydrocarbon insecticides and some



other pesticides thought to act by entirely different mechanisms are not additive in their tumorigenic effects may be related to the fact that, whereas all chlorinated hydrocarbon insecticides induce microsomal enzymes, they do so in different ways, as discussed in Section 15.2.2.3. Whatever the reason, the fact remains that the effects are not additive. Experiments in rats were carried out on combinations of Aramite, DDT, methoxychlor, and thiourea (three separate tests) and Aramite, DDT, methoxychlor, and aldrin (Radomski *et al.*, 1965; Deichmann *et al.*, 1967). In the final tests, each compound was fed separately at a dosage corresponding to 50% of its liver tumor-inducing dosage, and four compounds were fed in combination in such a way as to produce a total theoretical tumorigenic dosage of 200%. The authors concluded: "Considering the increased period of survival of rats fed mixtures no. 1 and no. 2 and the lower number of liver tumors produced in these rats, one cannot help but wonder whether the feeding of these mixtures produces an antagonistic type of effect" (Deichmann *et al.*, 1967).

**Discussion of Liver Changes in Rodents and Their Possible Significance for Humans** In spite of disagreement about interpretation of the liver cell changes, there is general agreement about their development and appearance. The change that can be detected first and can be produced by the smallest effective dosage involves the endoplasmic reticulum. The initial change is reversible but, even more important, it is especially pronounced in rodents. So far, there is no good evidence that anything from the first increase in endoplasmic reticulum to the final development of a highly nodular liver with occasional displacement of cells to the lung can be directly related to the health of humans.

One cannot accept uncritically the high degree of correlation between the ability of compounds to induce parenchymal liver tumors in mice and their ability to induce tumors in the liver and/or other organs of rats and hamsters. As demonstrated by Tomatis *et al.* (1973), this correlation is extremely good for compounds that are or are suspected of being carcinogens in humans but the correlation is poor for chlorinated hydrocarbon insecticides.

All available evidence indicates that humans do not appear to be susceptible to the tumorigenic action of the chlorinated hydrocarbon insecticides and phenobarbital. No increase in the occurrence of tumors has been found in heavily exposed populations. This includes groups of workers who manufacture and formulate DDT, dieldrin, aldrin, endrin, chlordane, and heptachlor and who have been examined carefully for tumors (Laws *et al.*, 1967; Jager, 1970; Vergsteeg and Jager, 1973; van Raalte, 1977; Wang and MacMahon, 1979a,b; Ditraglia *et al.*, 1981; Shindell *et al.*, 1981; Shindell and Ulrich, 1986; Ribbens, 1985).

Studies based on complete tumor registries indicate no increase of liver tumors attributable to phenobarbital among men and women who received heavy, essentially lifelong dosing with this drug for the control of epilepsy (Clemmesen *et al.*,

1974; MacMahon, 1985). In the United States, the total death rates for cancer of the liver and its biliary passages (classified individually as "primary," "secondary," and "not stated whether primary or secondary") lead to the conclusion that there has been a significant, almost constant decrease in the total rate of liver cancer deaths from 8.8 per 100,000 population in 1930 to 8.4 in 1944 (when DDT was introduced) to 5.6 in 1972. This almost constant decline in total liver cancer death rates over 42 years offers no evidence of any increase in liver cancer deaths since the introduction of the first organochlorine pesticide into the environment. The decrease in liver cancer deaths is even more significant in light of the increasing life span of the general population in the United States, which has resulted in an increased percentage of the population at risk from cancer over these years. In spite of the limitation inherent in the interpretation of such data, this record is a reminder that, more than 30 years after the introduction of DDT, there is no evidence whatsoever that DDT is carcinogenic in humans [Deichmann and MacDonald, 1976, 1977; World Health Organization (WHO), 1979; Higginson, 1985].

In the United States, the incidence of cancer is lower in rural counties than in metropolitan areas in general (Mason *et al.*, 1975). Actually, the highest nonoccupational storage of DDT in the United States has been measured in rural situations, largely as a result of local consumption of foods such as eggs that had high residues because of practices involving foods raised for local consumption only.

Sometimes it is implied that epidemiological evidence is useless for revealing the carcinogenicity of a material to humans unless it involves large numbers of people who have been exposed to the material for most or all of a lifetime. The fact is that some human carcinogens have been detected through their occurrence in high incidence in small groups for periods much less than 25 years. What is commonly considered the first recognition of chemical carcinogenesis in humans depended on the observations of a surgeon (Pott, 1775, 1790) in a small fraction of his patients. Such was the intensity of the exposure of the apprentices of chimney sweepers that cancer of the scrotum often appeared at puberty. In connection with tumors of the bladder caused mainly by  $\beta$ -naphthylamine but to a lesser degree by other aromatic amines, Hueper (1942, pp. 496–497) reviewed a series of cases in which the time from first exposure to recognition of symptoms was 8–41, 9–28, and 2–35 years, and in one series of 83 cases 71% of the tumors appeared from 1 to 15 years after exposure. Kleinfeld (1967) reported a 50–76% incidence of bladder cancer among several groups of workers. He also noted a sharp drop in incidence of this condition following decrease—but not discontinuation—of occupational exposure to  $\beta$ -naphthylamine. Thus heavy exposure to aromatic carcinogens may therefore produce cancer quickly. Hepatomegaly and induction of microsomal enzymes caused by chlorinated hydrocarbon insecticides do, however, occur in humans and may be slow to regress (Guzelian, 1985), so that for chemicals of this type other than DDT—for instance, BHC and chlordane—it may be too soon to be absolutely sure that they



are of no carcinogenic hazard to humans. For instance, a recent study of DDT, DDE, and  $\beta$ -BHC levels in ear wax collected from 3800 persons in the general populations of 35 Chinese counties showed a significant correlation between  $\beta$ -BHC levels and mortality rates from liver cancer, colon and rectal cancer, and lung cancer in males and colon cancer in females (Wang *et al.*, 1988).

In addition, it is worth remembering that in animals many of these insecticides are good promoters of liver cancer initiated by well-known carcinogens. Some of the areas of the world where DDT and lindane are used in large quantities are also areas where the risk of hepatocellular carcinoma is much greater than in the United States due to aflatoxin contamination of food or to carrying of the hepatitis B virus.

**Changes in Nonmicrosomal Enzymes** In addition to the important changes in microsomal enzymes caused by various chlorinated hydrocarbon insecticides, changes in nonmicrosomal enzymes have been documented. Among these enzymes are a number involved with gluconeogenesis (Karnik *et al.*, 1981). There is evidence that the first step in this process by DDT, chlordane, endrin, or heptachlor is stimulation of the cyclic AMP–adenylate cyclase system (Singhal and Kacew, 1976).

### 15.2.3.3 Other Toxic Effects

Besides affecting the liver and the nervous system, chlorinated hydrocarbon insecticides can cause disturbances of function in other tissues of experimental animals. These will be covered in the appropriate sections but include the thyroid (e.g., A. Singh *et al.*, 1985), which may lead to thyroid tumors (IARC, 1974, 1979, 1982, 1983). DDT and analogs have estrogenic effects (see Section 15.3.1.2) and, like the polyhalogenated aromatic chemicals, chlorinated hydrocarbon insecticides can accumulate in adrenals, causing various hormonal changes in the animal (Baggett *et al.*, 1980). Mirex will cause cataracts in fetuses and rat pups from dams treated with the chemical (Gaines and Kimbrough, 1970; Rogers and Grabowski, 1983) and many of these insecticides have effects on the immune system (Descotes, 1986), although whether this causes any adverse effects in the animal is unknown.

### 15.2.4 DIFFERENTIAL DIAGNOSIS

Poisoning caused by chlorinated hydrocarbon insecticides is acute whether caused by single or repeated doses. Of course, animals may be kept in a state of continuing illness by carefully chosen repeated doses. However, animals that survive recover promptly when dosage is discontinued. The same appears to be true of humans.

Human poisoning following massive accidental or suicidal exposure presents no problem of differential diagnosis. Diagnosis might be difficult if exposure were unrecognized and the

illness so mild that no convulsion occurred. However, any such illness would be brief and without sequel, so a failure of diagnosis would not be too serious.

If the fact of exposure is unrecognized in a case involving one or more convulsions, the differential diagnosis must involve (a) poisoning by a chlorinated hydrocarbon insecticide, (b) poisoning by some other kind of compound, including numerous drugs, (c) epilepsy, (d) convulsions secondary to infection, and (e) convulsions due to toxemia of pregnancy.

If substantial exposure to any chemical is suspected, every effort should be made to obtain samples that could confirm or refute a diagnosis of poisoning. This means that samples of vomit, stomach washings, urine and feces, blood, and food the patient was eating or materials actually used in preparing that food should also be saved for chemical analysis.

When it appears that convulsions are caused by a toxicant but the identity of the material is unknown, some hint of its nature may be obtained by careful observation of the patient. Convulsions caused by chlorinated hydrocarbon insecticides tend to appear early in the course of illness. The patient is unconscious during the convulsion, which resembles an epileptic fit except that no aura is present. The patient is left in a dazed state, but even during this period the vital signs are good, the immediate recovery is striking, and there is only a slight tendency for stimulation to induce a second convulsion. Convulsions caused by strychnine involve far more tonic spasm and opisthotonos than is ordinarily seen in poisoning by chlorinated hydrocarbon insecticides, and patients poisoned by strychnine remain conscious during the attack. Most convulsions associated with poisoning by organic phosphorus compounds occur late in the course of illness and are anoxic in origin. The patient is seriously ill before the convulsions begin, and the vital signs, especially respiration, are of poor quality. Of course, if convulsions continue and the patient's course is downhill, convulsions of any origin may be seen in a person with poor respiratory and cardiac function.

The presence of significant, febrile illness before the onset of convulsions tends to point to a diagnosis of infection. Fever can occur in connection with poisoning by chlorinated hydrocarbon insecticides (see Section 15.2.3.1), but it tends to start after convulsions, not before. Convulsions associated with infection are most common in babies still too young to explore and ingest poisons. In contrast, poisoning is most common between the ages of 1 and 3 years.

Poisoning by DDT is characterized by tremor early in the illness in a way that is not true of other chlorinated hydrocarbon insecticides (see Section 15.3.1.2). With this exception, it is essentially impossible to distinguish between the acute clinical pictures produced by sufficient dosages of the different chlorinated hydrocarbon insecticides without a history of exposure or analytical results.

The only chlorinated hydrocarbon insecticide that has caused chronic poisoning—but apparently no acute poisoning—is chlordane, for which the clinical picture is quite different (see Section 15.7.2.3).



### 15.2.5 TREATMENT OF POISONING IN HUMANS

The treatment of poisoning by a chlorinated hydrocarbon insecticide must be based mainly on general principles and on the results of animal experiments. Limited experience in treating human poisoning offers assurance that proper treatment is beneficial. However, there simply have not been enough properly treated cases of poisoning by chlorinated hydrocarbon insecticides to permit the kind of evaluation of therapy that has been possible in connection with organic phosphorus insecticides.

Whether first attention in a particular case is given to removal of the poison or to sedation must depend on the condition of the patient at the time.

#### 15.2.5.1 Removal of Poison

Of course, the initial dosage of any chlorinated hydrocarbon insecticide should be reduced as rapidly as circumstances permit. The importance of bathing, vomiting, cathartic, and other related procedures has been reviewed (Section 8.2.1), and the importance of supportive treatment has been discussed (Section 8.2.2). Oily laxatives should be avoided because they promote absorption of insecticide or solvent. However, nonabsorbable lipids may be of some use in hindering the absorption of lipophilic toxins including the chlorinated insecticides (Jan-dacek, 1982).

The ability of activated charcoal to absorb dieldrin and some other chlorinated hydrocarbon insecticides and thus promote their excretion in the feces following an acute dose is fully established. A few studies have indicated that activated charcoal (presumably by partially interrupting the enterohepatic circulation) can speed fecal excretion of stored dieldrin after dieldrin intake has stopped (Wilson and Cook, 1970).

Unfortunately, other studies failed to demonstrate any reduction of storage or increase in excretion associated with feeding of large doses of carbon (Fries *et al.*, 1970; Engebretson and Davison, 1971). The reason for the discrepancy in results is not evident. The charcoal used in some tests may not have been truly activated. In view of the proven effectiveness of phenobarbital and some other inducers of microsomal enzymes in speeding storage loss and excretion of several chlorinated hydrocarbon insecticides (Section 7.2.3), one certainly cannot consider successful use of these inducers in combination with charcoal as evidence for the effectiveness of charcoal (Braund *et al.*, 1971; Dobson *et al.*, 1971).

One must conclude that the treatment of people with activated charcoal is harmless, but its value, except in acute poisoning by certain compounds, is unproved in both animals and humans.

Plasmapheresis had no lasting effects on chlordecone levels in the blood of a poisoned patient (Guzelian, 1981) and hemoperfusion over various adsorbents was not an effective treatment, although promising results had been obtained *in vitro*

(Skalsky *et al.*, 1979). Hemoperfusion over XAO-4 has, however, produced promising results in a case of acute poisoning by lindane (Daerr *et al.*, 1985).

**Cholestyramine** At least one chlorinated hydrocarbon insecticide can be removed from the body selectively by oral administration of an anion exchange resin. Its practical use has been in chronic poisoning, but it should be equally or more effective in acute poisoning.

The fact that some compounds undergo enterohepatic circulation is well recognized (Section 3.2.4.2). This circulation has been demonstrated for several chlorinated hydrocarbon insecticides and probably occurs, for a greater or lesser period, with many or all others. However, it is only in connection with chlordecone that this phenomenon has been turned to therapeutic advantage. Having found evidence that only about 10% of chlordecone excreted in human bile is eliminated in the feces, Cohn *et al.* (1976) administered cholestyramine to seven patients at the rate of 24 gm/person/day for 3 days after having shown that the drug precipitates chlordecone from human bile *in vitro*. The treatment resulted in a 6.7-fold increase in fecal excretion. In 11 of 12 patients given 16 gm/person/day, disappearance of chlordecone from the blood was increased (compared to each person's rate before treatment), and the difference was significant in 7 of them. The average half-life of chlordecone in the blood was reduced from 165 to 80 days (Cohn *et al.*, 1978).

Choice of cholestyramine undoubtedly was based on the fact that it has been used successfully for years to increase the fecal excretion of bile acids, which, like chlordecone, are multiring compounds. The drug has been used in patients with pruritis due to partial biliary obstruction. Such patients have abnormally high levels of bile acids in their blood and tissues. It is thought that severe itching of some of the patients is the result of the high levels of bile acids in their skin.

Cholestyramine has a pH of 5–6. It is quite hydrophilic, but it is not soluble in water and is not hydrolyzed by digestive enzymes. Thus any compound bound to it is excreted with the feces.

Although the value of cholestyramine for promoting the fecal excretion of chlordecone was demonstrated first in people, it was considered prudent to study the matter in rats before using it very long for treating people. The rats received a single oral dose of [<sup>14</sup>C]chlordecone at the rate of 40 mg/kg. Cholestyramine produced an increase in the fecal excretion of radioactive material detectable within 24 hr. The total excretion of pesticide in the stool during 2 weeks of treatment was twice that of control animals, and treated animals killed at the end of this period contained 31–52% less radioactivity in different tissues and fluids than was true of the same tissues and fluids in controls (Boylan *et al.*, 1978).

Although chlordecone is the only pesticide whose excretion is known to have been promoted by cholestyramine, one must agree with Guzelian and co-workers (Cohn *et al.*, 1976; Boylan *et al.*, 1978; Guzelian, 1982a), who suggested that it might



be valuable for treating persons poisoned by other chlorinated hydrocarbon pesticides or even other lipophilic substances. Recent evidence showing that sucrose polyester in conjunction with caloric restriction reduced the body content of DDE in gerbils dosed with DDT suggests that this may be an alternative treatment for humans (Mutter *et al.*, 1988).

#### 15.2.5.2 Sedative and Anticonvulsive Therapy

The anticonvulsants that have been used most in treating poisoning by chlorinated hydrocarbon insecticides, in both patients and experimental animals, are pentobarbital and phenobarbital. It must be emphasized here that experiments in animals poisoned by dieldrin suggest that, for treating such poisoning in people, the drugs might have to be given at approximately twice the maximal rates used for other purposes. Such use is entirely safe as long as it achieves its objective of preventing convulsions and calming the patient without producing unconsciousness. Furthermore, it might be necessary to continue dosage with barbiturates at a high rate for 2 weeks or more. However, prolonged treatment has not proved necessary in human cases that have been described. It may be that people discontinue use and seek medical aid when their exposure is less and their illness milder than was true in the animal experiments just mentioned.

The value of barbiturates for promoting increased metabolism of chlorinated hydrocarbon insecticides remains unchallenged, and their use, even for this purpose alone, probably ought to continue. However, there is growing evidence for the use of diazepam for the control of convulsions. It is now regarded as the drug of choice for treating status epilepticus [American Medical Association (AMA), 1986]. It also has been used for treating convulsions caused by drugs and toxins. Experience in its use for treating poisoning by chlorinated hydrocarbon insecticides is limited.

The usual anticonvulsant dose of diazepam for adults is 5–10 mg administered slowly, intravenously. If convulsions make intravenous injection difficult, intramuscular injection may be substituted. Up to 10 mg/day may be given orally for maintenance. After convulsions have been controlled, diazepam should be discontinued gradually over a period of 2 or 3 days.

In at least two cases, paralysis combined with artificial respiration proved effective when anticonvulsants had failed. When endrin convulsions persisted every 15–20 sec in a 2-year-old girl in spite of large doses of phenobarbital, pentobarbital, and chloral hydrate, she was paralyzed by succinylcholine (0.5–1 mg/min, iv for 24 hr) while being maintained by mechanically assisted respiration with humidified 40% oxygen. Respiratory assistance was discontinued after an additional 8 hr. Improvement was gradual over a period of several days; recovery was complete (Hayden *et al.*, 1965).

Another case involved a 21-year-old man who ingested dieldrin at the rate of 120 mg/kg. Unconsciousness, cyanosis, and fits occurred before treatment was possible. An endotracheal tube was passed and gastric lavage was performed, but only a negligible amount of dieldrin was recovered. Mannitol (200 ml

of a 20% solution) was left in the stomach to induce catharsis. Metachlopramide (10 mg) was administered intravenously. A total of 60 mg of diazepam was given intravenously to control convulsions. The patient was then transferred to another hospital where more definite treatment was possible. When he arrived there 3.5 hr after ingesting dieldrin, he was still unconscious; his pulse was 120/min and his blood pressure was 180/120 mm Hg. There was no focal neurological deficit, but he had further convulsions while undergoing assessment, and he was given an additional 20 mg of diazepam. However, in the intensive care unit, profound muscular paralysis with pancuronium bromide was necessary before convulsions could be controlled sufficiently to allow adequate intermittent positive pressure ventilation. The paralysis was maintained for 48 hr before being withdrawn gradually, and it was supplemented with conventional anticonvulsive agents (phenobarbital 200 mg every 4 hr intramuscularly and phenytoin 100 mg every 6 hr, with 10-mg doses of diazepam intravenously as necessary). Intermittent positive pressure ventilation was used for 3 days. The rapid pulse and high blood pressure were considered due to sympathetic overactivity; 5 hr after admission, 10 mg of practolol intravenously reduced the pulse rate to 100/min and the blood pressure to 130/90 mm Hg. Propranolol (10 mg orally, every 6 hr) was administered for a further 60 hr to maintain a degree of  $\beta$ -sympathetic blockade. Rectal temperature remained between 38 and 39°C for much of the first 48 hr despite surface cooling by fanning and evaporation. On day 5, the patient was transferred to a general medical ward, but anticonvulsive medication was maintained for another 2 days. Poor memory and some persistent headaches were the patient's only complaints when he was seen on days 10 and 24. In spite of his bland affect at this time, he was severely disturbed psychologically, but whether this was the cause or effect of his self-poisoning was uncertain (Black, 1974).

Other sedatives (paraldehyde and chloral hydrate) have been used in cases of poisoning in humans with apparent benefit. However, there is no experimental evidence indicating that they are equal or superior to barbiturates.

Calcium gluconate is reported to control convulsions in experimental animals caused by some chlorinated hydrocarbon insecticides. It has appeared helpful in a few human cases. Since the mechanism of action is entirely different, it may be used in addition to sedatives and anticonvulsants.

Epinephrine is contraindicated. It sensitizes the heart, predisposing to serious arrhythmias and thus to death.

Regardless of what pharmacological antidote may be used, attention must be given as required to the general care of the patient (Section 8.2.2.9), use of oxygen (Section 8.2.2.2), maintenance of the airway, and artificial respiration (Section 8.2.2.1) if required.

Sometimes the insecticides may be used as solutions in organic solvents. The toxicity of the solvent should of course also be taken into account if a poisoning of this kind occurs. Jaeger *et al.* (1984) have reported six cases of poisoning by lindane–solvent mixtures. Diazepam was sufficient to control convulsions in five cases but vomiting and pulmonary edema in



some of the patients was thought to be due to the solvent (benzene) and not to lindane.

## 15.3 DDT AND ITS ANALOGS

### 15.3.1 DDT

DDT came to widespread attention because it dramatically controlled typhus and malaria in time of war. When it became available for civilian use, it controlled flies and other pests that annoy large numbers of people and may transmit disease, and it increased the production of important crops. Knowledge that traces of it are stored in essentially everyone in the world kept DDT in the spotlight. Later it was implicated in the injury of a wide variety of wildlife. Under these circumstances it is no wonder that DDT has been studied more thoroughly than any other pesticide and in more diverse relationships than any drug. By necessity, information on DDT was used to illustrate many principles and concepts discussed in Volume 1, including some very important matters such as human exposure levels and effects on domestic and wild animals that are not touched on in the present volume. In the following discussion some other subjects including details of storage and excretion of DDT in humans are covered, and there remains much to say about this fascinating compound.

#### 15.3.1.1 Identity, Properties, and Uses

**Chemical Names** *p,p'*-DDT, in Chemical Abstracts, is 1,1'-(2,2,2-trichloroethylidene)-bis(4-chlorobenzene). Common nomenclatures that have been used are 1,1,1-trichloro-2,2-

bis(*p*-chlorophenyl)ethane, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, and 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane. Because the older terminology has been used so widely in the past and many abbreviations are based on it (e.g., *p,p'*-DDT and *o,p'*-DDT), the *o* and *p* nomenclature will be used in this chapter for referring to DDT in its abbreviated form.

**Structure** The structure of *p,p'*-DDT and the structures of several of its analogs are shown in Table 15.2. The table is confined to compounds that occur in commercial DDT and analogs that have had some use as insecticides. It must be emphasized that even the commercially available insecticidal analogs have strikingly different properties. Especially remarkable are the slow metabolism and marked storage of DDT and its metabolite DDE and the rapid metabolism and negligible storage of methoxychlor.

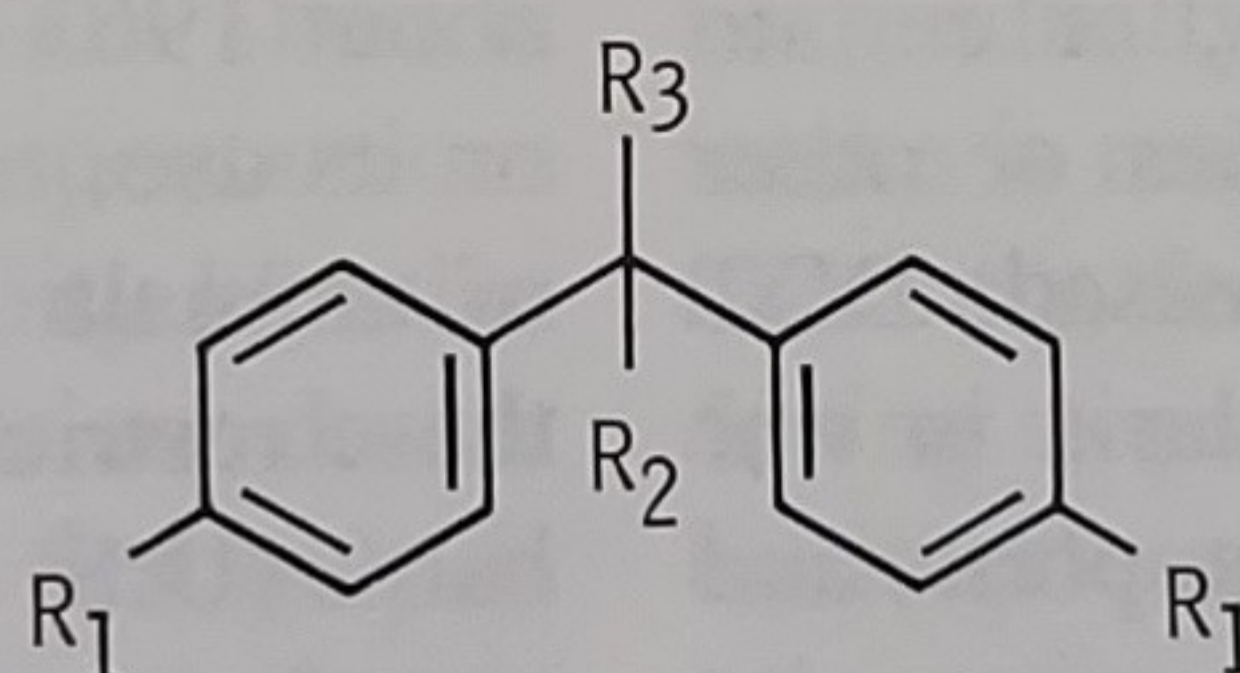
No attempt has been made to include in Table 15.2 the tremendous range of compounds that have been synthesized and studied in connection with structure-activity relationships, often with the hope of emphasizing the good properties of DDT and reducing its undesirable properties. For a more extensive consideration of analogs, see Metcalf (1973).

The formation of metabolites is considered under the heading Metabolism in Section 15.3.1.2.

**Synonyms** DDT apparently is universally accepted as the common name of the insecticide identified above. The term has been in use longer than official agencies for approving common names have existed or at least longer than these agencies have shown an interest in pesticides. As approved by BSI, DDT refers to the technical product, and there is historical

**Table 15.2**

Structure of *p,p'*-DDT and a Few of Its Analogs That Have Had Commercial Use



| Name                             | Chemical name <sup>a</sup>                      | R <sub>1</sub>                  | R <sub>2</sub> | R <sub>3</sub>                                      |
|----------------------------------|---|---------------------------------|----------------|---|
| DDT                              | 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane  | Cl                              | H              | Cl <sub>3</sub>                                     |
| Bulan <sup>b</sup>               | 2-nitro-1,1-bis(4-chlorophenyl) butane          | Cl                              | H              | CH(NO <sub>2</sub> )CH <sub>2</sub> CH <sub>3</sub> |
| chlorfenethol (DMC)              | 1,1-bis(4-chlorophenyl) ethanol                 | Cl                              | OH             | CH <sub>3</sub>                                     |
| chlorobenzilate                  | ethyl 4,4'-dichlorobenzilate                    | Cl                              | OH             | COOCH <sub>2</sub> CH <sub>3</sub>                  |
| chloropropylate                  | isopropyl 4,4'-dichlorobenzilate                | Cl                              | OH             | COOCH(CH <sub>3</sub> ) <sub>2</sub>                |
| DFDT                             | 1,1,1-trichloro-2,2-bis(4-fluorophenyl) ethane  | F                               | H              | CCl <sub>3</sub>                                    |
| dicofol (Kelthane <sup>®</sup> ) | 2,2,2-trichloro-1,1-bis(4-chlorophenyl) ethanol | Cl                              | OH             | CCl <sub>3</sub>                                    |
| ethylan (Perthane <sup>®</sup> ) | 1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane    | CH <sub>2</sub> CH <sub>3</sub> | H              | CHCl <sub>2</sub>                                   |
| methoxychlor                     | 1,1,1-trichloro-2,2-bis(4-methoxyphenyl) ethane | OCH <sub>3</sub>                | H              | CCl <sub>3</sub>                                    |
| Prolan <sup>b</sup>              | 2-nitro-1,1-bis(4-chlorophenyl) propane         | Cl                              | H              | CH(NO <sub>2</sub> )CH <sub>3</sub>                 |
| TDE <sup>c</sup>                 | 1,1-dichloro-2,2-bis(4-chlorophenyl) ethane     | Cl                              | H              | CHCl <sub>2</sub>                                   |

<sup>a</sup> See Section 15.3.1.1, Chemical Names. The names used here are those which are commonly encountered.

<sup>b</sup> A mixture of Prolan and Bulan (1 : 2) has been sold in the past as Dilan<sup>®</sup>.

<sup>c</sup> As an insecticide, this compound has the approved name of TDE; as a metabolite of DDT it usually is called DDD. It has been sold under the name Rhothane<sup>®</sup>; as a drug, the *o,p'*-isomer is called mitotane.



justification for that practice because DDT is an acronym for dichlorodiphenyltrichloroethane. *p,p'*-DDT is approved by BSI as a separate term. Zeidler (1874) called the compound dimonochlorophenyltrichloräthan. When used as a drug, DDT is known in the United Kingdom as dicophane (BP), in Sweden as klorfenoton, and in the United States as chlorphenothane (USP).

DDT has been sold under a variety of trade names, including Anofex<sup>®</sup>, Cesarex<sup>®</sup>, Didimac<sup>®</sup>, Digmar<sup>®</sup>, Dinocide<sup>®</sup>, Genitox<sup>®</sup>, Guesarol<sup>®</sup>, Gyron<sup>®</sup>, Ixodex<sup>®</sup>, Neocid<sup>®</sup>, and Zerdane<sup>®</sup>. Code designations for DDT include OMS-16 and ENT-1,506. The CAS registry number for *p,p'*-DDT is 50-29-3.

**Physical and Chemical Properties** DDT has the empirical formula  $C_{14}H_9Cl_5$  and a molecular weight of 354.49.

Pure *p,p'*-DDT is a white, tasteless, almost odorless crystalline solid melting at 108.5 to 109.0°C. Technical DDT is a waxy solid.

A typical example of technical DDT had the following composition: *p,p'*-DDT, 77.1%; *o,p'*-DDT, 14.9%; *p,p'*-DDD, 0.3%; *o,p'*-DDD, 0.1%; *p,p'*-DDE, 4.0%; *o,p'*-DDE, 0.1%; and unidentified compounds, 3.5%. The vapor pressure of DDT is  $1.5 \times 10^{-7}$  mm Hg at 20°C. DDT is highly soluble in apolar organic solvents: solubility per 100 ml acetone, 58 gm; ethanol, 2 gm; benzene, 106 gm; carbon tetrachloride, 45 gm; cyclohexanone, 116 gm; ethyl ether, 28 gm; petroleum ethers and kerosene, 4–10 gm. It is practically insoluble in water.

**History** DDT was first synthesized by Zeidler (1874). However, it was put to no use until its insecticidal properties were discovered by Paul Müller in 1939. The Swiss patent was issued in 1942.

The first sample sent to the United States arrived there in September 1942. This sample was tested for effectiveness and safety. The results were so encouraging that manufacture was given high priority. At first, the entire production was used for the protection of troops against malaria, typhus, or certain other vector-borne diseases, or against biting flies or other insects that are merely pests. As the supply increased, DDT was used in the United States for control of malaria in war areas, that is, in the vicinity of military installations, ports, and transportation centers. As a result of this effort, mosquito transmission of malaria was brought to an end in the United States in 1953, even though military personnel and other infected persons from the tropics continued to reintroduce the disease extensively as late as 1972 and in diminishing numbers thereafter.

The revolution in the control of malaria and typhus among allied troops and among certain civilian populations during World War II was accomplished with relatively little DDT. Far greater amounts were required for the control of agricultural and forest pests that became possible after the compound was released in the United States for commercial use on August 31, 1945. Civilian use in other countries became possible a little later, first largely on the basis of importation and gradually on the basis of local manufacture.

**Formulations and Production** Technical DDT has been formulated in almost every conceivable form including solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles, charges for vaporizers, and lotions. Aerosols and other household formulations often are combined with synergized pyrethrins.

Production and use of DDT in the United States have been discussed in Section 1.5.

Quantities of DDT and related compounds used in or sold for agricultural purposes in various countries in 1970 were as follows (tonnes): Australia (1000.0), Austria (20.5), Botswana (2.0), Canada (287.0), Ceylon (16.6), Columbia (980.0), Czechoslovakia (270.0), Egypt (3457.0), El Salvador (466.0), Federal Republic of Germany (152.0), Finland (6.1), Ghana (0.3), Guatemala (380.0), Hungary (20.6), Iceland (0.3), Israel (10.0), Italy (2178.0), Japan (401.0), Khmer (46.8), Kuwait (0.2), Madagascar (176.0), Ryukyu Islands (0.3), Sudan (269.0), Upper Volta (1.5), and Uruguay (5.0) [Food and Agriculture Organization (FAO), 1972]. These values total 10,146.2 tonnes. Thus, at least until 1970 the use of DDT was extensive on a worldwide basis but varied greatly from one country to another. A worldwide production of 60,000 tonnes for 1974 has been estimated (WHO, 1979), but there do not appear to be any figures for DDT production since then.

**Changing Patterns of Use** Before 1945, all of the DDT produced in the United States was used or allocated by the military services for various medical and public health uses. Early in 1945 it became available for rather extensive experimental work in agriculture, and it was commercially available in limited quantities early in the autumn of the same year (U.S. Department of Agriculture, 1945a,b). The results were so spectacular that use increased until 1959. In response to a demand for exports, production continued to increase until about 1963. Even before 1963 some restrictions were placed on its use, mainly to minimize residues in food and in the feed of animals that produce milk and meat. Among the first of these restrictions was that on its use on dairy cattle or in dairy barns (U.S. Department of Agriculture, 1949). Another important factor reducing the use of DDT was the increasing resistance of pests. One of the first species to be affected was the housefly; because of its abundance and widespread distribution, its resistance was bound to be noticed by the public generally. Although many pests of public importance have been resistant to DDT in some or all of their range, resistance among vectors of malaria has been minimal. Because malaria control constitutes such a large segment of vector control, the use of DDT for vector control has tended to remain stable, while its use in agriculture continued to decline, especially in temperate climates.

When Sweden banned DDT in March 1969 (to become effective January 1, 1970), they did so objectively, pointing out that "the need for insecticides is rather small in Sweden compared to that in many other countries" and that the ban of this



and certain other chlorinated hydrocarbon insecticides could be used as a tool to explore scientific problems about their movement in the environment. The safety of the chlorinated hydrocarbon insecticides under actual conditions of use was emphasized (Hayes, 1969).

In order to respond to ecologists who considered that the widespread occurrence of DDT in the environment was inherently bad and was the direct cause of injury to certain fish and birds, government agencies of some other countries attempted to justify restrictions on the use of DDT by its alleged threat to human health. This did not prevent the same agencies from providing that DDT might be used, if needed, to combat any future threat from vector-borne disease within their boundaries.

As the situation now stands, although many countries severely restrict the use of DDT, it is still used extensively, for both agriculture and vector control, in some tropical countries. Information apparently is not available on how much of the agricultural use involves food protection or how much loss of food production would result if use of DDT were discontinued. How much of the use of DDT is in public health is also unknown, but the picture with malaria control is clear. According to WHO in 1971, substitution of malathion or propoxur for DDT would increase the cost of malaria control approximately 3.4- and 8.5-fold, respectively, and this increase could not be supported in some countries without a decrease in the coverage of control programs. If DDT were not used, vast populations in the malarious areas of the world would be condemned to the frightening ravages of endemic and epidemic malaria (WHO, 1979).

### 15.3.1.2 Toxicity to Laboratory Animals

**Symptomatology** The description of DDT intoxication in animals given by Domenjoz (1944) remains one of the best. The first perceptible effect is abnormal susceptibility to fear, with violent reaction to normally subthreshold stimuli. There is definite motor unrest and increased frequency of spontaneous movements. As poisoning increases, hyperirritability like that seen in strychnine poisoning develops, but convulsions do not appear at this time. A fine tremor, recognizable at first only as a terror reaction, is later present as an intention tremor in connection with voluntary movement, is then present intermittently without observable cause, and is finally present as a coarse tremor without interruption even for several days. Spontaneous movement is limited, and food intake stops so that surviving animals lose weight. In the later stages, especially in some species, there are attacks of epileptiform, tonic-clonic convulsions with opisthotonos.

All the signs are strengthened by external stimuli and become manifest at first through external stimuli. In all stages, the animals show normal position and labyrinth reflexes. The picture of poisoning in mammals recalls the disturbances of movement and tone that are known in human pathology as the amyostatic syndrome.

Symptoms appear several hours after oral administration of

the compound, and death follows after 24–72 hr. The latent period after intravenous administration at about the LD 50 level is approximately 5 min; signs of poisoning reach a maximal level in about 30 min, and survivors are symptom-free in 18–24 hr. Animals that survive recover completely.

In addition to the features of poisoning already mentioned, Cameron and Burgess (1945) noticed that as rats, guinea pigs, and rabbits become sick they become cold to the touch and show ruffled fur. Some show diarrhea. These authors found that muscular tremors were preceded by muscular weakness which occurred first in the back and later in the hind legs. The front legs were relatively spared so that animals showing marked weakness of the hindquarters could still drag themselves about. However, several authors have found that the tremor characteristic of DDT poisoning generally starts in the muscles of the face, including the eyelids, and spreads caudally with variable severity until all the muscles are affected. Furthermore, although weakness of hindquarters has been seen by others, it is not a common finding.

Although there is a general similarity in the clinical effects of DDT in all vertebrate species, some characteristic differences exist. Cats show greater extensor rigidity and opisthotonos than other laboratory animals. The stiffness appears first in the distal part of the extremities and later extends to the proximal part and to the trunk. Poisoned cats show marked pilomotor activity. Convulsions in them may become almost continuous. Convulsions are also prominent in dogs, as is ataxia. Tremors are so pronounced in rats that it may be difficult to detect clonic convulsions in them. Rats poisoned by DDT show a reddish color about the eyes. The color has been attributed to excessive secretion of a porphyrin by the hard-erian glands and can occur when rats are ill from many other causes.

Poisoning produced by repeated doses of DDT differs from that produced by a single dose only insofar as the animal may be gradually debilitated, especially by malnutrition. If food intake is maintained, tremor may last for weeks or even, intermittently, for months. If the animals survive a short time after dosing stops, recovery is complete. However, food intake may be interfered with in at least two ways. Tremor and more severe signs may interfere mechanically with eating. Animals offered food containing high concentrations of DDT often eat little or nothing and lose weight rapidly. However, the same animals will show excellent appetites when offered the same kind of food containing no DDT just after refusing the major portion of their daily ration of contaminated food. Unlike dieldrin and some other compounds, DDT seems to have little effect on appetite as mediated by the central nervous system; it has a great deal to do with taste.

Animals that have suffered severe weight loss as a result of DDT poisoning may die partly as a result of general debility. At least in some colonies they have become prey to secondary infection.

In summary, animals that die as the result of repeated large doses of DDT and small animals that die as a complication of



**Table 15.3**  
Acute Oral and Dermal LD 50 of DDT to Animals<sup>a</sup>

| Species    | Formulation                | Oral<br>(mg/kg) | Dermal<br>(mg/kg) |
|------------|----------------------------|-----------------|-------------------|
| Rat        | water suspension or powder | 500–2500        | 1000              |
|            | oil solution               | 113–450         | 250–3000          |
| Mouse      | water suspension or powder | 300–1600        | 375               |
|            | oil solution               | 100–800         | 250–500           |
| Guinea pig | water suspension or powder | 2000            | 1500              |
|            | oil solution               | 250–560         | 1000              |
| Rabbit     | water suspension or powder | 275             | 375               |
|            | oil solution               | 300–1770        | 300–2820          |
| Dog        | water suspension or powder | >300            |                   |
|            | oil solution               |                 |                   |
| Cat        | water suspension or powder | 100–410         |                   |

<sup>a</sup> Modified from Hayes (1959a).

starvation following many somewhat smaller doses of DDT show the same signs as those seen in animals killed by one or a few large doses. Even though severely ill, animals that survive a few days after the last of many doses of DDT go on to recovery.

**Response to a Single Dose** Table 15.3 summarizes the acute oral and dermal toxicity of DDT to common laboratory animals, and Table 15.4 summarizes the subcutaneous, intravenous, and intraperitoneal toxicity. Both tables are condensed from an earlier review (Hayes, 1959a), which gives references and additional details. The values include those of Gaines (1960). It may be concluded that dissolved DDT is absorbed by

**Table 15.4**  
Acute Subcutaneous, Intravenous, and Intraperitoneal LD 50 of DDT to Common Laboratory Animals<sup>a</sup>

| Species    | Formulation                | Subcutaneous<br>(mg/kg) | iv<br>(mg/kg) | ip<br>(mg/kg) |
|------------|----------------------------|-------------------------|---------------|---------------|
| Rat        | water suspension or powder | >2000                   |               |               |
|            | oil solution               | 200–1500                | 47            | 80–200        |
| Mouse      | water suspension or powder | 1000–1500               |               |               |
|            | oil solution               | 300                     |               |               |
| Guinea pig | water suspension or powder |                         |               |               |
|            | oil solution               | 900                     |               | 150           |
| Rabbit     | water suspension or powder |                         |               |               |
|            | oil solution               | 250–>3200               | 30–41         | <2100         |
| Dog        | water suspension or powder |                         |               |               |
|            | oil solution               |                         | 68            |               |
| Cat        | water suspension or powder |                         |               |               |
|            | oil solution               | <650                    | 32            |               |
| Monkey     | water suspension or powder |                         |               |               |
|            | oil solution               |                         | 55            |               |

<sup>a</sup> Modified from Hayes (1959a).

all portals, although DDT powder is absorbed through the skin to only a negligible degree. It is frequently impossible to put enough DDT dust on the skin of animals to kill them, so that an LD 50 value for this formulation cannot be determined by the dermal route. Although formulation is important in determining the toxicity of DDT by other routes, the difference is not so great as it is in connection with skin exposure. In round figures, DDT is about 4 times more toxic when given intravenously than when given orally and about 40 times more toxic intravenously than dermally.

In general, DDT, like some other lipophilic chemicals, appears more toxic orally as a solution in vegetable oil or animal fat than when given in some petroleum fractions. Petroleum may act as a laxative. The heavier fractions are never absorbed, and DDT dissolved in such fractions has to be extracted from the solvent in order to show toxicity.

In summary, DDT is a compound of moderate acute toxicity. Compared with other chlorinated hydrocarbon insecticides of equal or greater toxicity, it is remarkable in being little absorbed by the skin.

Acute oral LD 50 values of DDT metabolites commonly found in tissues or excreta are shown in Table 15.5. Readily absorbable formulations of the metabolites are less toxic than the most absorbable preparations of the parent compounds (cf. Table 15.3).

At an oral dosage of 150 mg/kg, *p,p'*-DDT produces severe illness in all rats and kills about half of them, but *o,p'*-DDT at the same dosage produces no illness, even though the concentrations of the two compounds in the brain at various intervals after dosing are about the same. At a dosage of 3000 mg/kg, *o,p'*-DDT produces mild to moderate illness, and the concentration in the brain is 5–9 times the concentration of *p,p'*-DDT necessary to produce similar symptoms. Thus, *p,p'*-DDT appears to be inherently more toxic than the *o,p'* isomer (Dale *et al.*, 1966a).

**Table 15.5**  
Oral LD 50 Values of Metabolites of DDT

| Compound and species   | LD 50<br>(mg/kg) | Reference                          |
|------------------------|------------------|------------------------------------|
| <b>DDE<sup>a</sup></b> |                  |                                    |
| rat, M                 | 880              | Gaines (1960)                      |
| rat, F                 | 1240             | Gaines (1960)                      |
| mouse                  | 700              | von Oettingen and Sharpless (1946) |
| mouse                  | 1000             | Domenjoz (1946a,b)                 |
| <b>DDD<sup>b</sup></b> |                  |                                    |
| rat, M                 | >4000            | Gaines (1969)                      |
| <b>DDA<sup>c</sup></b> |                  |                                    |
| rat                    | 1900             | Smith <i>et al.</i> (1946)         |
| rat, M                 | 740              | Gaines (1960)                      |
| rat, F                 | 600              | Gaines (1960)                      |
| mouse                  | 720              | von Oettingen and Sharpless (1946) |
| mouse                  | 590              | Domenjoz (1946a,b)                 |

<sup>a</sup> 1,1-Dichloro-2,2-bis(4-chlorophenyl)ethylene.<sup>b</sup> 1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane.<sup>c</sup> 2,2-Bis(4-chlorophenyl)acetic acid.



**Table 15.6**  
Effect of Age on the Toxicity of DDT to Rats

| Number of doses | Age <sup>a</sup> | LD 50 (mg/kg) <sup>b</sup> | Reference                       |
|-----------------|------------------|----------------------------|---------------------------------|
| 1               | newborn          | >4000                      | Lu <i>et al.</i> (1965)         |
| 1               | newborn          | 2356                       | Harrison (1975)                 |
| 1               | 10 days          | 728                        | Henderson and Woolley (1969)    |
| 1               | 14–16 days       | 437                        | Lu <i>et al.</i> (1965)         |
| 1               | weanling         | 355                        | Lu <i>et al.</i> (1965)         |
| 1               | 2 months         | 250                        | Henderson and Woolley (1969)    |
| 1               | 2 months         | 152                        | Mitjavila <i>et al.</i> (1981a) |
| 1               | 3–4 months       | 194                        | Lu <i>et al.</i> (1965)         |
| 1               | middle-aged      | 235                        | Lu <i>et al.</i> (1965)         |
| 1               | adult            | 225                        | Harrison (1975)                 |
| 1               | preweaning       | 279                        | Lu <i>et al.</i> (1965)         |
| 4               | adult            | 285                        | Lu <i>et al.</i> (1965)         |

<sup>a</sup> Data from more than one strain of rat.

<sup>b</sup> Total intake of one or more doses.

Rats tolerate higher tissue levels of DDA than of DDT. Eighteen hours after intravenous injection of DDA at a rate of 100 mg/kg, tissue levels still were higher than are usually found in animals fatally poisoned by DDT (Judah, 1949). DDA produces somewhat less injury than DDT to the liver but, especially at high intravenous dosages, produces greater damage to the kidney (Lillie *et al.*, 1947). This is consistent with the finding of Spicer *et al.* (1947) that, following administration of DDT, DDA constitutes a higher proportion of DDT-related compounds in the kidney (25%) than in any other tissue, being 12% in the liver, 10% in the brain, and even less in other tissues.

Young animals eat more than adults in relationship to their body weight. For this and other reasons, young animals often are more susceptible than adults to poison in food. However, young animals are inherently less susceptible to certain compounds. There is no evidence that DDT is more toxic to young animals of any species, including humans, and in the rat the young are less susceptible to a single dose (Table 15.6). They are about equally susceptible to repeated doses, as shown in the same table. According to Henderson and Woolley (1969), the relative insusceptibility of the young is associated with relatively poor absorption of DDT by their central nervous systems and by lesser inherent susceptibility of the young brain to DDT already absorbed by it. Further study by the same authors (Henderson and Woolley, 1970) showed that fatal poisoning of both 10- and 60-day-old rats involves hyperexcitability and intense tremor followed by prostration and eventual respiratory failure. However, in the adult rat, DDT causes convulsions, an increase in respiration and heart rate, and a lethal increase in body temperature (40–42°C) prior to death, but the body temperature of the immature rat decreases during acute intoxication by DDT. The authors suggested that, whereas DDT is a direct depressant of respiration in both young and old rats, the additional toxic responses manifested by seizures and hyperthermia account for the increased lethality of DDT in mature animals. No acute LD 50 could be

established for hamsters (Agthe *et al.*, 1970), which also seem resistant to chronic effects of DDT (Table 15.7).

There is virtually no sex difference in the acute toxicity of DDT to rats; the LD 50 is 113 and 118 in males and females, respectively (Gaines, 1960). A similar situation is observed with mice (Agthe *et al.*, 1970). When DDT is fed to rats at ordinary dietary levels, the two sexes store it equally. However, at higher dosages, females store more of the compound; the difference is explained mainly by the lesser activity of the liver microsomal enzymes in female rats and only in part by relatively higher food intake of the females.

**Response to Repeated Doses** The effects of repeated doses of DDT are summarized in Table 15.7.

The 90-dose oral LD 50 of technical DDT in rats is 46.0 mg/kg/day (Gaines, 1969). The chronicity index is 5.4. Thus the compound has only a moderate tendency to cause cumulative effects, and this limited tendency is fully explained by the accumulation of DDT itself in tissues as a result of continuing intake. In fact, this accumulation, which is strictly dosage dependent, is detectable at all measurable levels of intake. The relationship in humans is shown in Fig. 7.4.

If storage is considered undesirable *per se*, then DDT is without a no-injurious-effect level. However, the same may be said for all compounds that are absorbed, for the presence of all of them in the bodies of exposed organisms—perhaps at very low levels and for relatively short periods—may be assumed; failure to demonstrate low levels of storage does not depend on physiology but only on limitations of the analytical techniques employed.

A number of papers have reported no-effect levels for DDT within parameters other than storage, namely: rat, 0.05 mg/kg/day (Lehman, 1951, 1952); dog, 8 mg/kg/day (Lehman, 1951, 1952); and monkey, 2.2–5.54 mg/kg/day (Durham *et al.*, 1963).

There remain reports of effects in animals at the lowest dosages investigated. For example, decreased serum albumin and increased  $\beta$ - and  $\alpha$ -globulins in the blood of rats and rabbits maintained on a dosage of 0.2 mg/kg/day for 3–11 months were reported by Kagan *et al.* (1969), but these changes are unconfirmed.

In summary, the lowest dosages that have been studied in animals are of the same order of magnitude as those encountered by people who make or formulate DDT and, therefore, hundreds of times greater than the dosages encountered by ordinary people. The animal studies have continued long after a steady state of storage has been achieved. The results permit the conclusion that bioaccumulation sufficient to produce neurotoxicity or other clinical effects, including a reduction of the life span, can occur only at dosage levels substantially higher than those encountered by the most heavily exposed workers. DDT dosages encountered by workers produce in some groups of mice and rats a small but detectable increase of the liver changes (hypertrophy, margination, and lipospheres) characteristic of rodents. The same changes occur in low incidence in control mice and rats but not in other animals.



**Table 15.7**  
Effect on Various Animals of Prolonged Oral Administration of DDT

| Dosage               |                                      |   |                     |   |   |
|----------------------|--------------------------------------|---|---------------------|---|---|
| Range<br>(mg/kg/day) | Method and<br>concentration<br>(ppm) | Species, <sup>a</sup><br>number,<br>and sex | Maximum<br>duration | Results   | References                              |
| 41-80                | 800 ppm in diet                      | rat   | 2 yr                | increased mortality, typical liver changes, and liver carcinomas            | Fitzhugh and Nelson (1947) <sup>b</sup> |
|                      | 46 mg/kg, then 140 ppm in diet       | mouse<br>36 M, 36 F                         | 1.5 yr              | hepatomas in 51 and 21% of M and F compared with 18 and 0.6% of controls    | Innes <i>et al.</i> (1969)              |
|                      | 1000 ppm in diet                     | hamster<br>25 M, 30 F                       | 1.9 yr              | no liver tumors and survival slightly less than controls                    | Agthe <i>et al.</i> (1970)              |
|                      | 1000 ppm in diet                     | hamster<br>30 M, 30 F                       | 1.5 yr              | no liver tumors but decreased serum cholinesterase                          | Graillot <i>et al.</i> (1975)           |
|                      | 1000 ppm in diet                     | hamster<br>35 M, 36 F                       | 2.4 yr              | no liver tumors and survival as controls                                    | Rossi <i>et al.</i> (1983)              |
|                      | 3200 ppm in diet                     | dog<br>10                                   | 4 yr                | 100% mortality; liver damage, no tumors                                     | Lehman (1951-1952; 1965)                |
|                      | 5000 ppm in diet                     | monkey<br>1 M                               | 10 wk               | 100% mortality  | Durham <i>et al.</i> (1963)             |
|                      | 50 mg/kg/day                         | monkey<br>6                                 | 14 wk               | 100% mortality; no hematologic effects                                      | Cranmer <i>et al.</i> (1972)            |
| 21-40                | 400 ppm in diet                      | rat<br>24 M, 12 F                           | 2 yr                | increased mortality, typical liver changes                                  | Fitzhugh and Nelson (1947) <sup>b</sup> |
|                      | 500 ppm in diet                      | rat<br>37 M, 35 F                           | 2.9 yr              | liver tumors in 45%   | Rossi <i>et al.</i> (1977)              |
|                      | 500 ppm in diet                      | rat<br>38 M, 38 F                           | 2.3 yr              | liver tumors in 18% F   | Cabral <i>et al.</i> (1982b)            |
|                      | 250 ppm in diet                      | mouse<br>103 M, 90 F                        | 2 gen               | risk of liver tumor increased 3.7- and 18.5-fold in M and F, respectively   | Tomatis <i>et al.</i> (1972)            |
|                      | 250 ppm in diet                      | mouse<br>31 M, 121 F                        | 2 gen               | liver tumors in 48 and 59% of M and F                                       | Terracini <i>et al.</i> (1973)          |
|                      | 500 ppm in diet                      | hamster<br>39 M, 40 F                       | 1.7 yr              | no liver tumors and survival as controls                                    | Cabral <i>et al.</i> (1982a)            |
|                      | 2000 ppm in diet                     | dog<br>4                                    | 4 yr                | 25% mortality; minor liver damage but no tumors                             | Lehman (1951-1952; 1965)                |
|                      | 100 ppm in diet                      | mouse<br>100 M, 100 F                       | 2 yr                | hepatomas increased in F of one strain but no increase in hepatocarcinomas  | Fitzhugh (1970)                         |
| 11-20                | 100 ppm in diet                      | mouse<br>30 M, 30 F                         | 2 yr                | risk of liver tumors increased 4.4-fold                                     | Walker <i>et al.</i> (1973)             |
|                      | 100 ppm in diet                      | mouse<br>30 M, 3 F                          | 2 yr                | risk of liver tumors increased 3.3- and 4.2-fold in M and F                 | Thorpe and Walker (1973)                |
|                      | 50 ppm in diet                       | mouse<br>127 M, 104 F                       | 2 gen               | risk of liver tumors increased 2.45- and 3.46-fold in M and F, respectively | Tomatis <i>et al.</i> (1972)            |
| 6-10                 | 50 ppm in diet                       | mouse<br>30 M, 30 F                         | 2 yr                | Risk of liver tumors increased 2.9-fold                                     | Walker <i>et al.</i> (1973)             |
|                      | 400 ppm in diet                      | dog<br>2                                    | 4 yr                | no effect   | Lehman (1951-1952; 1965)                |
|                      | 20 ppm in diet                       | mouse<br>48 M, 128 F                        | 2 gen               | no increase in tumors   | Terracini <i>et al.</i> (1973)          |
| 1.26-2.5             | 200 ppm in diet                      | monkey                                      | 7.5 yr              | no effect   | Durham <i>et al.</i> (1963)             |
|                      | 10 ppm in diet                       | mouse<br>104 M, 124 F                       | 2 gen               | risk of liver tumors increased 2.26- and 2.46-fold in M and F, respectively | Tomatis <i>et al.</i> (1972)            |
| 0.63-1.26            | 25 ppm in diet                       | rat   | 2 yr                | no clinical effect; M survived longer than controls                         | Treon and Cleveland (1955)              |
| 0.31-0.63            | 10 ppm in diet                       | rat   | 2 yr                | typical liver changes; no effect on reproduction                            | Fitzhugh (1948)                         |
|                      | 12.5 ppm in diet                     | rat   | 2 yr                | no effect   | Treon and Cleveland (1955)              |

(continued)



Table 15.7 (Continued)

| Dosage    | Method and concentration (ppm) | Species, <sup>a</sup> number, and sex | Maximum duration | Results  | References                     |
|-----------|--------------------------------|---------------------------------------|------------------|--|--------------------------------|
|           | 2.8–3.0 ppm in diet            | mouse 683                             | 5 gen            | tumors in 28.7%, including lung carcinomas, lymphomas, and leukemias | Tarján and Kemény (1969)       |
| 0.16–0.31 | 2 ppm in diet                  | mouse 124 M, 111 F                    | 2 gen            | risk of liver tumor doubled in M, unchanged in F                     | Tomatis <i>et al.</i> (1972)   |
|           | 2 ppm in diet                  | mouse 58 M, 135 F                     | 2 gen            | no increase in tumors  | Terracini <i>et al.</i> (1973) |
| 0.08–0.16 | 2.5 ppm in diet                | rat                                   | 2 yr             | no effect  | Treon and Cleveland (1955)     |

<sup>a</sup> Various strains of rats were used; Osborne–Mendel (Fitzhugh and Nelson, 1947), Carworth (Treon and Cleveland, 1955), Wistar (Rossi *et al.*, 1977), MRC–Porton (Cabral *et al.*, 1982b). Mouse strains used were (C57BL/6 × C3H/Anf)F1 and (C57BL/6 × AKR)F1 (Innes *et al.*, 1969), CFI (Tomatis *et al.*, 1972; Thorpe and Walker, 1973; Walker *et al.*, 1973), BALB/cJ and C<sub>3</sub>HeB/FeJ (Fitzhugh, 1970), BALB/c (Tarján and Kemény, 1969; Terracini *et al.*, 1973).

<sup>b</sup> Slides reexamined by Reuber (1978).

**Absorption** Most DDT dust is of such large particle size that any that is inhaled is deposited in the upper respiratory tract and eventually is swallowed (see Section 3.2.2.4). Toxicity data indicate that respiratory exposure to DDT is of no special importance.

Review of the early literature indicates that the absorption of DDT from the gastrointestinal tract is slow. Whereas intravenous injection at the rate of 50 mg/kg produces convulsions in rats in 20 min, convulsions occur only after 2 hr when DDT is administered orally at a rate two or more times the LD 50 value. The onset of convulsions is delayed for about 6 hr when DDT is given to rats orally at approximately the LD 50 value (Dale *et al.*, 1963).

Early studies based on toxicity indicated that DDT dissolved in animal or vegetable fats is absorbed from the gastrointestinal tract about 1.5–10 times more effectively than is undissolved DDT. This has been confirmed in a number of studies, e.g., Keller and Yearly (1980) and Palin *et al.* (1982). There was also evidence that large doses of the compound in the gastrointestinal tract were poorly absorbed from nonabsorbable solvents. At high dosage levels, less [<sup>14</sup>C]DDT is absorbed and stored in organs following oral than following intraperitoneal administration, and a higher proportion is excreted in the feces than after intraperitoneal administration (40 versus 0.9%) (Bishara *et al.*, 1972). However, in connection with small repeated doses, the presence or kind of solvent made little difference; apparently the occurrence of bile in the intestine and the presence of some fat in the diet are sufficient to promote absorption of the compound.

Rothe *et al.* (1957) reported that after giving radioactive DDT by stomach tube as an emulsion of a peanut oil solution they were able to recover 41–57% of it in lymph drained from the animal by means of a cannula in the thoracic duct. Less than 0.1% of the activity was found in the urine, 7.4–37.1% was found in the feces or in the intestinal contents when the animals were killed, and 19–67% of the activity was found in the carcass. The total dose accounted for analytically varied

from 89 to 118%; thus, recovery was complete within the accuracy of the method. Of the administered DDT not found in feces and intestinal contents, 47–65% was found in the lymph. The animals that withstood the operation best had peak lymph flows of nearly 6 ml/hr. In these animals, DDT was absorbed at rates as high as 381 µg/hr; the highest rate of absorption was reached in 2–3 hr and was markedly reduced by the fourth hour after intubation. Fifty percent of the DDT-derived material found in the lymph was absorbed in the first 2.5–7 hr, and 95% was absorbed by 18 hr. Because the lymphatic duct in the rat is not a single vessel, Rothe *et al.* (1957) were unable to exclude the possibility that some or all of the DDT that they later recovered from the carcasses of their animals had been transported to the general circulation by collateral lymph vessels rather than by the hepatoportal system. They gave indirect evidence for supposing that little or no DDT is absorbed from the gastrointestinal system by the blood, and this has been confirmed by Palin *et al.* (1982). However, dieldrin is a similar compound, and only a small proportion of it administered as a peanut oil solution is absorbed by the lymph (Heath and Vandekar, 1964). The reason for the marked difference in the absorption of the two compounds is unknown.

Most of the DDT absorbed into the lymph is carried in the lipid core of chylomicrons and thence into the plasma proteins (Pocock and Vost, 1974; Sieber *et al.*, 1974). *p,p'*-DDT is taken up at a rate which is different from those of its metabolites and *o,p'*-DDT (Sieber, 1976) and which does not strictly parallel differences in lipid solubility.

As already stated, dermal absorption of DDT is very limited.

**Distribution and Storage** A detailed review of the literature (Hayes, 1959a) shows that a number of facts about the distribution and storage of DDT were established early either by single, classical papers now fully confirmed or by correlation of contributions from several laboratories. The major results may be summarized as follows.



1. DDT is stored in all tissues. Storage of the compound in blood, liver, kidney, heart, and the central nervous system was reported by Smith and Stohlgan (1944).
2. Higher concentrations of DDT are usually found in adipose tissue than in other tissues (Ofner and Calvery, 1945).
3. Rats store DDT in their fat at all accurately measurable dietary levels, including the unintended residues in standard laboratory feeds.
4. Following repeated doses, storage in the fat increases rapidly at first and then more gradually until a peak or plateau is reached (Laug *et al.*, 1950). It was recognized that repeated doses at a moderate rate could result in greater total storage of DDT in the fat than a single dose at the highest rate that can be tolerated or even a single dose at a rate that frequently is fatal.
5. By plotting animal data published no later than 1950, it was possible to show that when other factors are kept constant the equilibrium storage of DDT in each tissue varies directly with the daily dosage (Fig. 2.13).
6. However (with the apparent exception of the dog), storage in the fat and perhaps in other tissues is less extensive in relation to dosage at higher dietary levels (Fig. 2.13).
7. The rat apparently tends to lose a part of the DDT it has stored in fat at the peak level reached in about 6 months, even though continued on the same diet (Laug *et al.*, 1950).
8. There is a measurable difference between the storage patterns of different species; that of the dog differs most (Fig. 2.13).
9. At higher dosage levels but not at ordinary residue levels the female rat consistently stores more DDT in its fat than the male when offered the same diet. The difference is accounted for only in part by the greater food intake of the female and must depend partly on more rapid biotransformation in the male. Other species show little or no sex difference.
10. The amount of DDT stored in the tissues is gradually reduced if exposure to the compound is discontinued or diminished.

It is interesting to note that even in the early studies there was satisfactory agreement between different authors and, in fact, between different laboratories. Later studies have amplified some of the findings.

More recent observations regarding storage include the finding that rats whose brains contain DDT at a concentration of 25 ppm or less (wet weight) usually survive, whereas higher levels tend to be fatal regardless of whether absorption followed one or many doses. The danger level is approximately the same in several species of birds (see Section 3.2.3.4). Of samples that may be collected from a living animal, the concentration of DDT in serum most accurately reflects its concentration in the brain, the critical tissue.

Adams *et al.* (1974) observed that about the same con-

centrations of DDT and related compounds are stored by male rats and by females that reproduce successfully. The lower storage in mated females probably is accounted for by transfer to the young via the placenta and the milk. However, other factors may be involved; no one really has accounted for the disposal of the increased DDT taken in by the female rat as a result of her high food intake during lactation.

When DDT, some of its analogs, and several other chlorinated hydrocarbon insecticides were fed to male and female rats for four generations, there was little variation in storage of the materials from one generation to another and no evidence of a continuing increase in succeeding generations (Adams *et al.*, 1974).

The concentrations of DDT in the blood and other tissues of the fetus are lower than those in corresponding tissues of the mother (Dedek and Schmidt, 1972).

The simultaneous administration of DDT and aldrin or of DDT and dieldrin may alter the storage of DDT or the other agent, or both. The effect varies from one species to another, as discussed in Section 15.2.2.3.

Studies of the distribution of DDT in various lipid fractions that are based on tissue extracts obtained with one or more organic solvents, like those of Kuz'minskaya *et al.* (1972a), are difficult to interpret because there is no way to determine how much of the material initially was associated with protein.

DDE constitutes about 4% of technical DDT. Most species convert some of the DDT they ingest to DDE. Finally, most species, including humans, store DDE more tenaciously than they do DDT, the greater part of which is metabolized by a different pathway from that of DDA and excreted more rapidly. The result is that DDE, expressed as a percentage of total DDT-related compounds, increases in individuals after DDT intake decreases and increases in successive steps of the food chain.

The Rhesus monkey apparently is an exception. Monkeys store DDE when it is fed to them. However, when feeding is stopped, the rate of loss of DDE stored in fat is more rapid than that of DDT (Durham *et al.*, 1963). Whether it is relative inability to form DDE, unusual ability to excrete it, or a combination of both that accounts for the fact that little or no DDE can be found in monkeys fed DDT is not entirely clear.

**Metabolism** The chemical nature of the chief metabolite excreted in the urine was first elucidated by White and Sweeney (1945). Rabbits were given DDT melting at 107–108°C at a rate of 100 mg/kg/day, 6 days/week, and their urine was collected. It contained a considerable amount of organic chloride, whereas normal rabbit urine did not. The authors isolated a crystalline material containing 25.36% chlorine and melting at 166–166.5°C, which was shown to be 2,2-bis(4-chlorophenyl)acetic acid (DDA). The product obtained from urine was identical to that synthesized from glyoxylic acid and chlorobenzene and with a compound obtained through the chemical degradation of DDT. Only 80–85% of the total organic chloride of the rabbit urine was found soluble in alkali and bicarbonate. For this and other reasons, it was considered pos-



sible that DDA was not the only chlorinated organic compound present.

Later work by many authors has amply confirmed that DDA isomers are the major urinary metabolites of *p,p'*-DDT and *o,p'*-DDT in all mammals, including humans. It may be added that in spite of great strides in analytical chemistry, the nature of all excreted metabolites may not have been elucidated fully.

The ability of phenobarbital and especially diphenylhydantoin to promote the excretion of DDT was discovered in humans (Davies *et al.*, 1969) and later confirmed in animals (Cranmer, 1970; Alary *et al.*, 1971; Fries *et al.*, 1971).

The fact that DDE is stored in tissue was first demonstrated in connection with human fat (Pearce *et al.*, 1952; Mattson *et al.*, 1953). The authors did not know whether the compound resulted from partial degradation of DDT residues on plants or whether the DDE was formed during the process of digestion or after absorption. It is now known, using modern methods, that some of our food contains DDE but that humans are capable of forming the product from DDT.

That portion of the metabolism of DDT that leads to DDA in rats was explored by Peterson and Robinson (1964), who gave evidence for the sequence of changes leading to DDA involving reduction to 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (DDD) followed by dehydrochlorination to 1-chloro-2,2-bis(4-chlorophenyl)ethene (DDMU), which was apparently converted to 2,2-bis-(4-chlorophenyl)ethanol (DDOH) via 2,2-bis(4-chlorophenyl)ethene (DDNU). The compound identified by Peterson and Robinson (1964) as a "probable" intermediate aldehyde between *p,p'*-DDOH and *p,p'*-DDA was later synthesized and shown to be highly labile (McKinney *et al.*, 1969), confirming the guess by Peterson and Robinson that it is unlikely to accumulate in tissues in measurable amounts. Kujawa *et al.* (1985) have obtained evidence for its formation from *p,p'*-DDD by rat liver homogenates and its presence in the urine of rats injected with DDD. Abou-Donia and Menzel (1968) identified two additional metabolites, bis(*p*-chlorophenyl)methane (DDM) and bis(*p*-chlorophenyl) methyl ketone (DBP) in chicken eggs and young chicks. Not only was DBP found to result from the metabolism of DDA with DDM as an intermediate, but DBP was the only metabolite of DDE administered directly to eggs or chicks.

Organ perfusion studies indicated that the liver is capable of biotransformation of DDT, DDE, DDD, DDMU, and other possible metabolites (Datta and Nelson, 1970). Cultures of human embryonic lung cells are capable of metabolizing DDT to DDA via DDD (North and Menzer, 1973).

When DDA was discovered, it was postulated on chemical grounds that DDE was a step in its formation (White and Sweeney, 1945); however, rats which produced both DDE and DDA from DDT were said by Peterson and Robinson (1964) to be incapable of forming DDA when fed preformed DDE. This finding was contradicted by Datta (1970) and by Datta and Nelson (1970), who claimed that <sup>14</sup>C-labeled *p,p'*-DDE was converted by rats to 1-chloro-2,2-bis(4-chlorophenyl)ethene (*p,p'*-DDMU), which then underwent further metabolism to *p,p'*-DDA. Datta suggested that the predominance of detoxica-

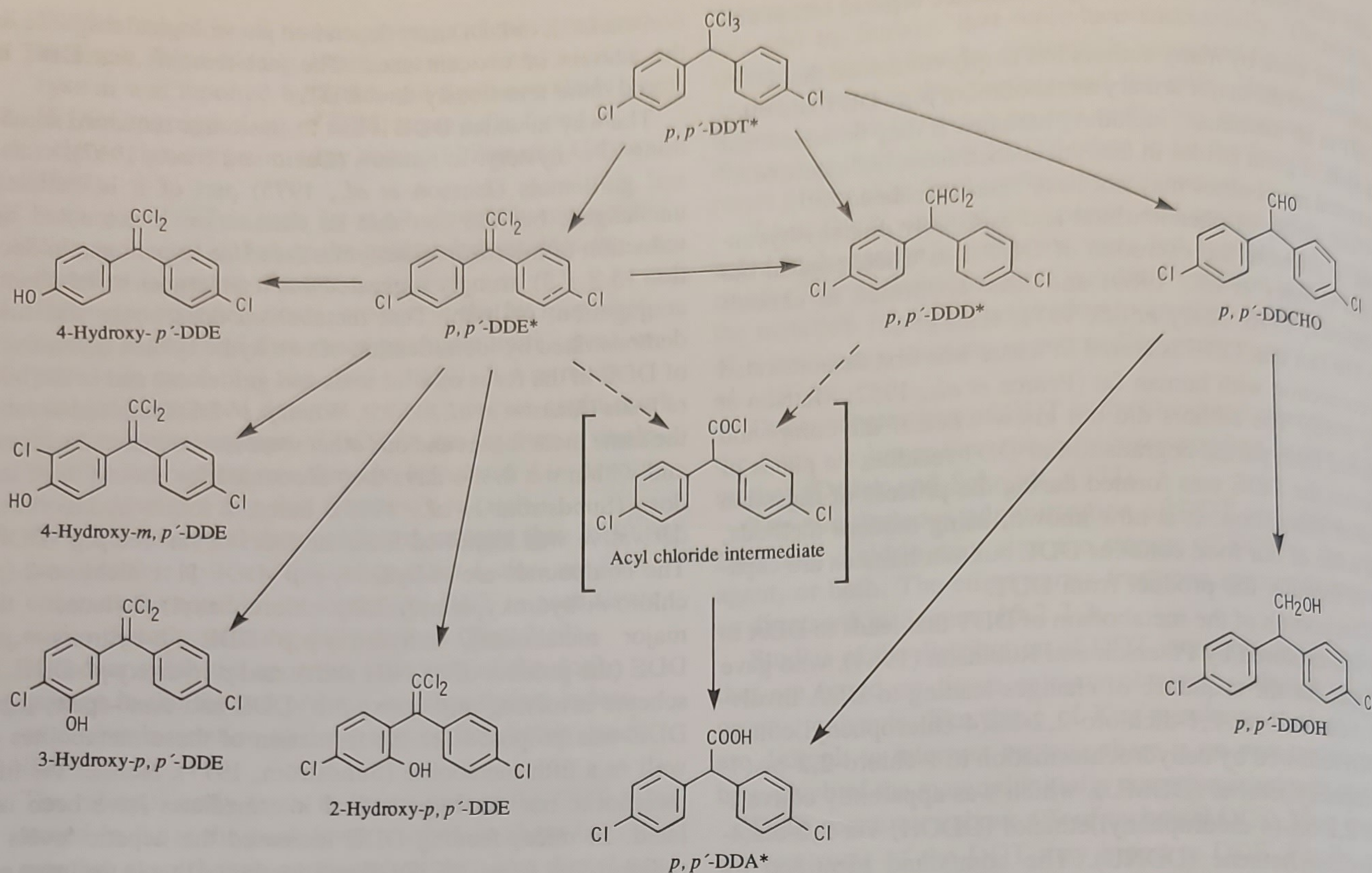
tion via DDE or DDD may depend on physiological response or the amount of toxicant used. The fact remains that DDE is stored more tenaciously than DDT.

The way in which DDE is lost from storage remained something of a mystery. In humans (Cueto and Biros, 1967), seals, and guillemots (Jansson *et al.*, 1975) part of it is excreted unchanged, but the fact that its elimination is promoted by induction of microsomal enzymes (see Use Experience in Section 15.3.1.3) strongly suggested that it undergoes metabolism, conjugation, or both. That metabolism does occur was first demonstrated by identification of two hydroxylated derivatives of DDE in the feces of wild seals and guillemots and in the bile of seals (Jansson *et al.*, 1975). When *p,p'*-DDE was fed to rats, the same metabolites and one other were isolated from the feces, and within the first 6 days they accounted for about 5% of the dose (Sundström *et al.*, 1975). Later, a fourth hydroxylated derivative was identified from the feces of rats fed *p,p'*-DDE. The compounds are *m*-hydroxy-*p,p'*-DDE [1,1-dichloro-2-(*p*-chloro-*m*-hydroxyphenyl)-2,2(*p*-chlorophenyl)ethylene, the major metabolite], *o*-hydroxy-*p,p'*-DDE, *p*-hydroxy-*m,p'*-DDE (the product of an NIH shift), and *p*-hydroxy-*p'*-DDE. A scheme involving *m,p*-epoxy-*p,p'*-DDE and *o,m'*-epoxy-*p,p'*-DDE was proposed for the formation of these metabolites as well as a fifth metabolite (Sundström, 1977). Neither the fifth metabolite nor the hypothetical intermediates have been isolated. In mice, feeding DDE increased the hepatic levels of radioactivity from [<sup>14</sup>C]DDE and decreased that in the urine and feces (Gold and Brunk, 1986). The only metabolite identified was the *o*-hydroxylated product.

DDE is metabolized not only to easily excretable phenols but also to *m*-methylsulfone-*p,p'*-DDE. In the blubber of seals from the Baltic, this compound was found in a concentration of 4 ppm along with DDE (138 ppm), DDD (10 ppm), DDT (78 ppm), and various polychlorinated biphenyls (PCBs) and their metabolites (150 ppm) (Jensen and Jansson, 1976). Sulfur-containing metabolites of halogenated aliphatic and aromatic chemicals usually arise by initial conjugation with glutathione. The possibility of glutathione-derived conjugates of DDT seems to be a virtually unexplored field.

Because DDT causes liver tumors, particularly in mice (See Table 15.7), some of the steps in its metabolism leading to reactive intermediates were studied with liver microsomal systems. The reductive dechlorination of *p,p*-DDT to DDD can occur with a cytochrome P-450 system, especially under anaerobic conditions (Hassall, 1971; Esaac and Matsumura, 1980; Zaidi, 1987). A one-electron reduction of DDT to the 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethyl radical seems to occur, followed by abstraction of a hydrogen atom, possibly from lipid, to give DDD (Kelner *et al.*, 1986). The reduction of DDT to DDD is stimulated by thiols in an unknown manner. The formation of an intermediate radical explains binding to microsomal lipid, especially under anaerobic conditions (Baker and Van Dyke, 1984). DDD, on the other hand, needs aerobic conditions for binding, implying that further metabolism is required. Other studies with mouse liver microsomes have shown the formation of 2,2-bis(*p*-chlorophenyl)-1,2-ethanediol





**Figure 15.1** Metabolites of *p,p'*-DDT and the postulated route of metabolism in the rat. The metabolites indicated by an asterisk have been found in humans.

(DDNU-diol) from DDNU, suggesting that a reactive epoxide intermediate might be formed (Planche *et al.*, 1979). When synthesized, however, the ethylene oxide (DDNU-oxide) was not mutagenic.

In a series of papers, Gold and colleagues examined the metabolism of DDT metabolites in mice *in vivo*. The results seem to be a little different from that previously accepted for rats. It is thought that DDMU can undergo epoxidation; the resulting mutagenic epoxide is hydrolyzed and oxidized to 2-hydroxy-2,2-bis(4-chlorophenyl)acetic acid ( $\alpha$ OH-DDA), which is excreted in the urine (Gold *et al.*, 1981; Gold and Brunk, 1982). Another route of metabolism of DDT in both the mouse and hamster (Gold and Brunk, 1982, 1983, 1984) seems to be the formation of DDA by a route involving hydroxylation on the C-1 side chain carbon of DDD (see Fig. 15.2). Loss of HCl gives an intermediate acyl chloride, 2,2-bis(4-chlorophenyl)acetyl chloride (Cl-DDA), capable of reacting with cellular proteins, DNA, etc. or losing water to give DDA.

Since this work, the metabolism of DDT in rats has been reexamined (Fawcett *et al.*, 1981, 1987) and seems to be similar to that described above for hamsters and mice. The conversion of *p,p'*-DDD to *p,p'*-DDA occurs primarily by hydroxylation leading to Cl-DDA, which on hydrolysis gives DDA. This acyl chloride may also be formed from DDE via an epoxidation route. Although DDMU is converted to DDA (Gold and

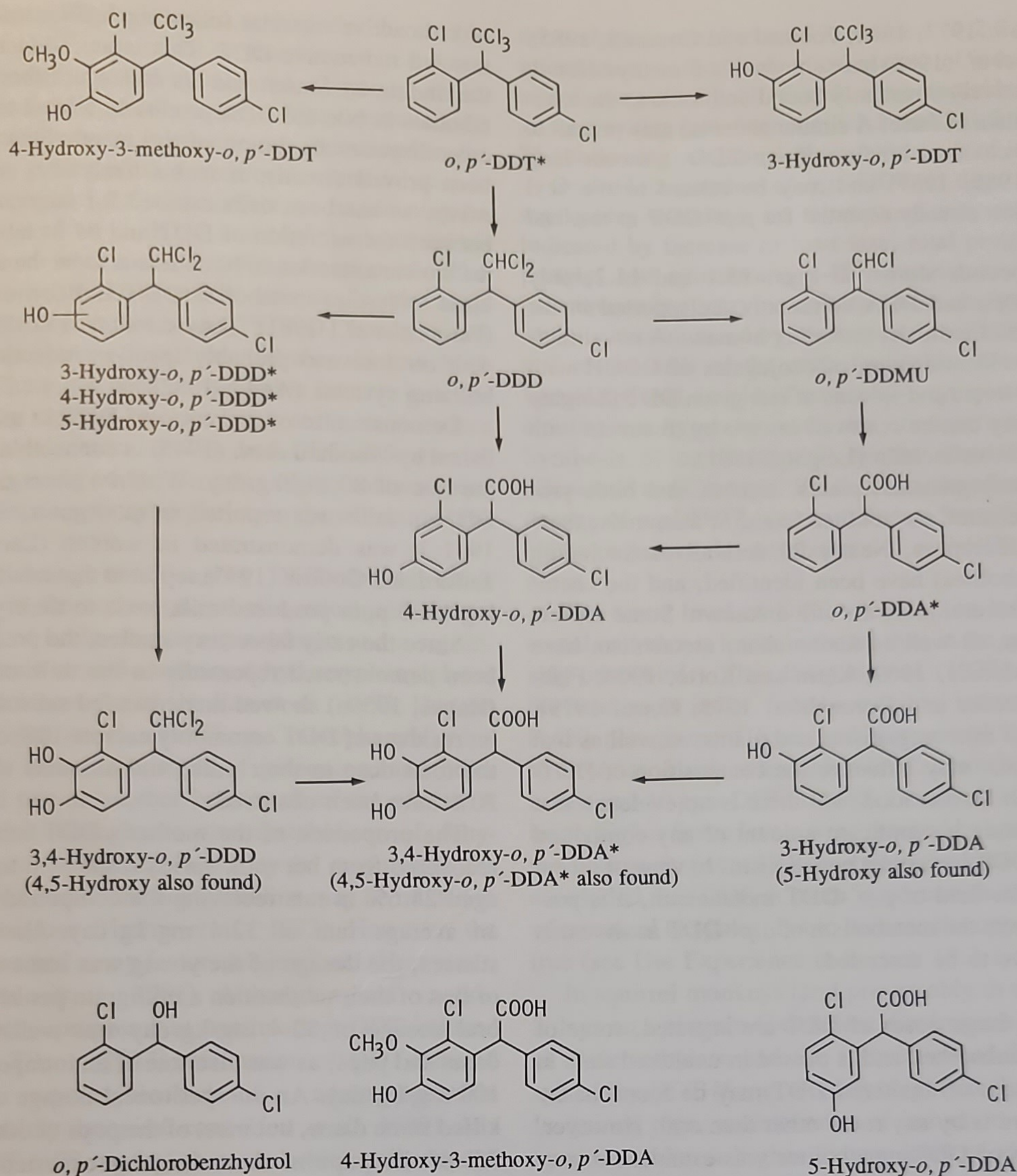
Brunk, 1984; Fawcett *et al.*, 1987), there is now considerable doubt as to whether it is an important intermediate in DDT metabolism. In addition, there is evidence to suggest that DDOH is a reduction product of DDCHO formed directly from DDT and not a precursor. A current scheme for the metabolism of *p,p'*-DDT in rats is shown in Fig. 15.1 and is still incomplete after nearly 40 years of study. However, it is possible that this will need to be amended. For instance, the role of DDOH still appears to be uncertain (Kujawa *et al.*, 1985).

The conversion of *o,p'*-DDT to *p,p'*-DDT has been reported (Klein *et al.*, 1965; French and Jefferies, 1969), but when the possibility was reinvestigated using  $^{14}\text{C}$ -labeled *o,p'*-DDT, no conversion could be detected (Cranmer, 1972). The chromatographic peak closely resembling that of *p,p'*-DDT observed in the earlier studies undoubtedly is the result of a metabolite of *o,p'*-DDT.

The opposite conversion, namely biotransformation of *p,p'*-DDT or *p,p'*-DDD to the corresponding *o,p'*-compounds, has been reported in chicken egg and young chicks (Abou-Donia and Menzel, 1968) but has not been confirmed.

Compared to *p,p'*-DDT, the more rapid excretion of *o,p'*-DDT is explained at least in part by the observed ring hydroxylation of the parent compound in rats (Feil *et al.*, 1973) and chickens (Feil *et al.*, 1975) and of its metabolite *o,p'*-DDD in rats (Reif and Sinsheimer, 1975) and humans (Reif *et al.*, 1974).





**Figure 15.2** Metabolites of *o,p'*-DDT and the main derivative *o,p'*-DDD in rats. The sequence of metabolism shown may have to be evolved in light of recent investigations of *p,p'*-DDT metabolism. Compounds indicated by an asterisk have been found in humans, including those humans treated with large doses of *o,p'*-DDD. In rats, glycine and serine conjugates of *o,p'*-DDA have been found in the urine, and the aspartic acid conjugate of *o,p'*-DDA has been found in the feces.

(see Fig. 15.2). At least 13 metabolites were detected in rats and 15 in chickens. Ring hydroxylation, which has not been observed with *p,p'*-DDT or *p,p'*-DDD (but has been seen with *p,p'*-DDE), was present in all species. There were, however, some species differences. For example, *o,p'*-DDE and three hydroxylated *o,p'*-DDEs were found in the excreta of chickens but not in the excreta of rats. In two patients with adrenal carcinoma for which they were receiving *o,p'*-DDD at a rate of 2000 mg/day, as much as 46–56% of the daily intake was recovered in the urine following acid hydrolysis. Just over half of the recovered material was in the form of *o,p'*-DDA, but the remainder was in the form of hydroxylated derivatives, specifically *m*-hydroxy-, *p*-hydroxy-, *m*-hydroxy-*p*-methoxy-, and *p*-

hydroxy-*m*-methoxy-*o,p'*-DDA. Some other hydroxylated compounds were found in trace amounts. All hydroxylation had occurred on the ring that had its chlorine in the *o* position (Reif *et al.*, 1974). When the metabolism of a single 100-mg oral dose of *o,p'*-<sup>14</sup>CDDD was studied in rats, averages of 7.1 and 87.8% of the activity were recovered in the urine and feces, respectively, within 8 days (Reif and Sinsheimer, 1975). The high recovery indicated rapid excretion with little storage.

*o,p'*-DDD is specifically toxic for the adrenal cortex in a number of species including humans. *In vitro* studies suggest that this is due to its activation in adrenal mitochondria to a metabolite which binds covalently. Unlike the situation in liver, a metabolite more polar than DDA is also produced



(Martz and Straw, 1977, 1980; Pohland and Counsell, 1985). Recently, Lund *et al.* (1988) have shown that 3-methylsulfonyl-*f,f*-DDE is selectively covalently bound and toxic to the adrenal zona fasciculata of mice. A similar situation may prevail to account for the covalent binding of *o,p*-DDD in mouse lung (Lund *et al.*, 1986, 1989) and may be related to the acyl chloride formation already reported for *p,p'*-DDT in rats and mice (Fig. 15.1).

Of the compounds shown in Figs. 15.1 and 15.2, only DDT, DDD, DDE, and DDA commonly are reported in the tissues or excreta of animals, including humans. A novel finding has been the identification of conjugates of DDOH with fatty acids in the livers and spleens of rats given DDT (Leighy *et al.*, 1980). They can be removed *in vivo* by treatment with bile salts, heparin, or lecithin (Leighy, 1981).

Although microorganisms, plants, insects, and birds produce many of the same metabolites found in mammals, there are interesting differences. Nearly 20 derivatives (including mammalian metabolites) have been identified, and the chemical structures of several more are still unknown. Some aspects of nonmammalian, as well as mammalian, metabolism have been reviewed (Menzie, 1969; Klein and Korte, 1970; Fishbein, 1974; Schroeder and Dorozalska, 1975; Korte, 1979). The metabolism of microorganisms and plants, as well as that of domestic animals, may influence the composition of DDT-derived residues in human food, but there is no evidence that these residues contain a significant amount of any compound not formed from DDT by human metabolism. In view of recent developments in the field of *p,p'*-DDT metabolism, it is possible that in the future the metabolism of *o,p'*-DDT as shown in Fig. 15.2 may have to be amended.

**Excretion** When large doses of DDT are ingested, some of the compound is unabsorbed and is passed in unaltered state in the feces. Only traces of unaltered DDT may be found in the feces when exposure is by any route other than oral. However, true fecal excretion of DDT metabolites was established irrespective of the route of administration (Hayes, 1965). In humans the ratio is obviously different. Although the excretion of DDT-related material in the feces of humans receiving 35 mg/person/day has been studied using colorimetry (Hayes *et al.*, 1956), this result has never been confirmed by gas chromatography, even in connection with workers whose exposure was heavy and prolonged (Hayes, 1982). Either DDT metabolites are not excreted by humans in the feces to any important degree, or they are excreted in one or more forms different from those already demonstrated in rats.

The bile appears to be the principal source of DDT metabolites in the feces of rats. When the bile duct was cannulated before intravenous injection of radioactive DDT, 65% of the dose was recovered in the bile, 2% in the urine, and only 0.3% in the feces (Jensen *et al.*, 1957), and the possibility of some contamination of the feces by urine could not be excluded.

The different routes of excretion are not unrelated. Burns *et al.* (1957) found that there was an increase in urinary excretion

of radioactive material following ligation of the bile duct in rats fed radioactive DDT. This is an indirect confirmation of the finding by Jensen and his colleagues that most of the metabolites in bile are DDA or closely related to it. Although an enterohepatic circulation of the metabolites of DDT has not been proved directly, it seems likely that such a circulation exists, as has been demonstrated for ethylan. The difference between the excretion of DDT and its metabolites in rats and the slower excretion in birds seems to be the reduced ability of birds to further metabolize DDE and convert DDD to DDA (Fawcett *et al.*, 1981). The excretion of DDE in rats is dependent on dose and probably involves induction of drug-metabolizing systems (Ando, 1982).

Demonstration of excretion of DDT in milk was first published by Woodard *et al.* (1945) in connection with a dog fed at the rate of 80 mg/kg/day. Within a short time, excretion of DDT in milk was reported in rats, goats, and cows, and in 1951 it was demonstrated in women (Lang *et al.*, 1951). Telford and Guthrie (1945) reported that rats fed a diet containing 1000 ppm produced milk toxic to their young.

Since the early laboratory studies, the presence of DDT has been demonstrated repeatedly in the milk of cows. A review (Hayes, 1959a) showed that cows fed substantial, but nontoxic, residues of DDT commonly excrete 10% or slightly more of the total dose in their milk, and amounts slightly more than 30% have been observed.

The proportion of the mother's DDT intake that could be recovered from her milk varied from 12.6 to 30.2% and averaged 24.6% in rats receiving the compound from their diet at an average rate of 32.4 mg/kg/day. Under these circumstances, the dosage of the young was somewhat less than half of that of their mothers on a milligram per kilogram basis. The oral dosage of 32.4 mg/kg/day was well tolerated by both dams and pups, as was also true of an intraperitoneal dosage of 100 mg/kg/day. An intraperitoneal dosage of 200 mg/kg/day killed some dams, but most of the pups of other dams survived. All of the pups of these mothers experienced reduced milk intake and reduced weight gain. The concentration of DDT in the brains of these pups was much lower than in pups killed by oral administration of the compound, indicating that the young of mothers receiving massive dosages of DDT suffer malnutrition but not poisoning (Hayes, 1976b).

Wilson *et al.* (1946) showed that DDT was secreted from the skin of a cow maintained on an oral dosage of about 53 mg/kg/day.

Because DDA is the main form in which DDT is excreted, it might be expected that, following its direct administration, DDA would be excreted relatively efficiently, and this is true. It was found very early that, during the first several days after oral dosing, rabbits excreted DDA in the urine approximately 15 times faster than animals given DDT at an equivalent dosage. Although the rate of DDA excretion increased somewhat, the rate of excretion associated with DDT increased more rapidly, so that the values differed by a factor of only 5 after day 20 of feeding (Smith *et al.*, 1946).



**Biochemical Effects** There is reason to think that the mechanism of action of DDT is its effect on membranes in the nervous system, especially axonal membranes. Certainly, action on membranes is a fundamental property of the compound. Its action on conductance in an inanimate membrane and in the membranes of the giant axons of cockroaches and lobsters is discussed in Section 4.1.2.3. The effect on axons may be related to inhibition of  $\text{Na}^+$ -,  $\text{K}^+$ -, and  $\text{Mg}^{2+}$ -adenosine triphosphatase derived from a nerve ending fraction of rabbit brain that is inhibited by DDT and is discussed in the same section. A similar enzyme that binds [ $^{14}\text{C}$ ]DDT has been isolated from the synapses of rat brain (Bratowski and Matsumura, 1972). There has been considerable interest in a Ca-ATPase which may regulate calcium levels at the axon surface (Ghiasuddin and Matsumura, 1979), and DDT is known to cause prolonged opening of the ion gates of the sodium channel perhaps by affecting phosphorylation in the  $\alpha$ -subunit protein (Ishikawa *et al.*, 1989).

At a supralethal dosage of 600 mg/kg, DDT caused in rats a marked decrease in the concentration of cortical and striatal acetylcholine and of brain stem norepinephrine and a significant increase in brain stem 3-methoxy-6-hydroxyphenylglycol and 5-hydroxyindoleacetic acid (Hrdina *et al.*, 1973; Hudson *et al.*, 1985; Tilson *et al.*, 1986). *p*-Chlorophenylalanine blocked all of the neurotoxic signs of poisoning, and other inhibitors blocked one or another but not all of the effects. It was concluded that changes in the metabolism of 5-hydroxytryptamine and norepinephrine may be responsible for DDT-induced hypothermia and acetylcholine may be related to tremors and convulsions (Hrdina *et al.*, 1973). However, the situation is complex and many factors are involved (Herr *et al.*, 1985, 1986; Hudson *et al.*, 1985). Although spinal  $\alpha$ ,-adrenoceptors have been proposed as modulating DDT-induced tremor (Herr and Tilson, 1987) attenuation of DDT-induced motor dysfunction requires blockade of  $\alpha$ , adrenoceptors in region other than solely the spinal cord (Herr *et al.*, 1989). At a lower dose of DDT (180 mg/kg), but one which still induced convulsive tremor, acetylcholine and cyclic GMP were increased in the cerebellum (Aldridge *et al.*, 1978). In adult rats and mice there is a decrease in the cholinergic muscarinic receptors of rat brain (Eriksson *et al.*, 1984), particularly in the cerebellum (Fonseca *et al.*, 1986). A particularly interesting finding is that the palmitic acid conjugate of DDOH can also have this effect (Eriksson and Nordberg, 1986). Disturbances of brain lipid metabolism have been observed in monkeys after chronic exposure to DDT (Sanyal *et al.*, 1986). Khaikina and Shilina (1971) reported that administration of DDT to rats at only one-fifth of the LD 50 for 20 days increased by 188% the amount of 5-hydroxyindoleacetic acid excreted in their urine. This indicated a change in the metabolism of serotonin, but probably does not support a serotonin deficiency as a DDT mode of action (Chung Hwang and Van Woert, 1981).

It is evident that many of the side effects of DDT are the result of its induction of microsomal enzymes. Both the dosage response and the morphological aspects and implications of

this induction are discussed in Section 15.2.3.2. Background information on the biochemical aspects of induction of microsomal enzymes by DDT and other pesticides has been reviewed earlier (see Sections 3.1.2 and 3.1.3 and Table 3.6). The following additional observations are of interest.

Oral administration of *o,p'*-DDT to dogs at a rate of 50 mg/kg/day stimulates the microsomal enzymes of the liver as indicated by increase in liver size, total protein, microsomal protein, and cytochrome P-450 concentration and by direct measurements of enzyme activity. These changes in the liver are initially accompanied by an increase in the size of the adrenals and of the cells of the zona fasciculata; these cells become vacuolated and devoid of acidophilic cytoplasm, and their nuclei become hyperchromatic and often peripheral in position. Synthesis of corticosteroids by the adrenal is not blocked (Copeland and Cranmer, 1974). Thus, the effect of a substantial dosage of *o,p'*-DDT is quite different from that of *o,p'*-DDD, although part of the metabolism of *o,p'*-DDT must be by that route.

The tissue level of DDE necessary to induce liver microsomal enzymes is lower in the rat than in the quail (and presumably other birds). Thus Bunyan *et al.* (1972), using residues in the heart as an index, found a maximal increase in cytochrome P-450 per gram of liver and a maximal activity of aniline hydroxylase levels at tissue levels of approximately 3 ppm DDE in rats and 40 ppm DDE in quail. However, at any given dietary level, higher tissue levels were reached by quail than by rats, so the dosage responses of the two were similar. These authors concluded that DDE is more important than DDT in inducing microsomal enzymes, but in humans the opposite appears to be true (see Use Experience in Section 15.3.1.3).

In squirrel monkeys (and presumably in other species) only 2 days on a vitamin C-deficient diet impairs both the induction of *O*-demethylase and the stimulation of the glucuronic acid system by DDT (5 mg/monkey/day) (Chadwick *et al.*, 1971b). In guinea pigs, maintenance of induction of microsomal enzymes requires a higher dietary level of vitamin C than does prevention of scurvy (Wagstaff and Street, 1971a).

The association of lipids with the function of microsomal enzymes is recognized generally, as is the fact that DDT induces these enzymes. Therefore, it might have been expected that DDT and essential fatty acids would interact. Tinsley and Lowry (1972) found that the growth of female rats receiving *p,p'*-DDT at a dietary level of 150 ppm was depressed if they received a diet deficient in essential fatty acids but was slightly stimulated if they received the same diet supplemented with these acids. Another parameter influenced by the same variables was the ratio of various liver lipids. The changes in fatty acid composition were related to the proliferation of hepatic smooth endoplasmic reticulum; it was suggested that DDT influenced essential fatty acid metabolism by increasing the demand for them. Sampson *et al.* (1980) found that DDT did not exacerbate aspects of essential fatty acid deficiency but did alter lipid metabolism in an unexplained way.

In contrast, a variety of diets (containing fats that may occur



in the human diet and that were in approximately the same proportion as fats in typical human food in the United States had little or no influence on the storage of DDT and a wide range of pesticides fed to rats for four generations in combination at rates only 200 times those found in the Market Basket Study of food in the United States (Adams *et al.*, 1974). Fat mobilization can cause rapid release of stored DDT, but this does not seem to be associated with any major toxic effect assessed pathologically or biochemically (Mitjavila *et al.*, 1981b).

DDT has been shown *in vitro* and sometimes *in vivo* to influence some enzymes of intermediary metabolism and other miscellaneous enzymes. For instance, DDT and a variety of analogs have been shown to affect isolated rat liver mitochondria but the significance of this *in vivo* is uncertain (Ohyama *et al.*, 1982). So far evidence is lacking that the degree of this inhibition in the intact organism is sufficient to have any influence on function.

The hyperglycemia observed during much of the early part of acute poisoning may be associated with an increase in four gluconeogenic enzymes (pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase). Increase in these enzymes in the renal cortex of rats has been observed after a single dose at a rate as low as 100 mg/kg or greater or following 45 daily doses at rates of 5 or 25 mg/kg/day. The changes are not mediated through release of corticosteroids from the adrenal glands (Kacew and Singhal, 1973). The fact that 100 mg/kg is the smallest single dosage that produced a statistically significant change in these enzymes indicates that their alteration is a complication rather than a cause of poisoning.

A review (Hayes, 1959a) of early literature indicates that high concentrations of DDT inhibit phosphatidase, muscle phosphatases, carbon anhydrase, and oxaloacetic carboxylase and increase the activity of cytochrome oxidase and succinic dehydrogenase. However, none of these changes with the possible exception of inhibition of carbonic anhydrase could be shown to have any connection with the toxic action of DDT or even with its side effects. Neal *et al.* (1944) reported a small but consistent increase in the volume of urine excreted in 24 hr when dogs were dosed orally or by insufflation at the rate of 100 mg/kg/day. No other change in the urine and no change in kidney function was demonstrated. The possibility that increased urinary output is related to the inhibition of carbonic anhydrase (Torda and Wolff, 1949) may deserve attention. However, reexamination of data from volunteers receiving 3.5 or 35 mg/person/day indicated no increase in urinary volume compared with controls (Hayes *et al.*, 1971).

On the other hand, many enzymes including plasma amylase, aldylase, glutamic-pyruvic transaminase, and isocitric dehydrogenase were not changed in squirrel monkeys given dosages from 0.05 to 50 mg/kg/day, the latter of which proved fatal within 14 weeks (Cranmer *et al.*, 1972).

**Effects on the Nervous System** The major toxic action of DDT is clearly on the nervous system, probably by slowing

down closing of "gates" in axon sodium channels (Dubois and Bergman, 1977; Woolley, 1982, 1985; Hong *et al.*, 1986), and it requires an intact organism for full expression. The fact that DDT causes a myotonic response in muscle and substitution of a train of spikes for the normal diphasic electroneurogram (Eyzaguirre and Lilienthal, 1949) is in marked contrast to the absence of detectable injury or, in fact, any response in other isolated tissues. As early as 1945, Lewis and Richards found DDT to be inert when it was exposed to tissue cultures of heart, kidney, stomach and intestine, liver, and muscle from 7- to 9-day chick embryos and of brain and spleen from a 1-day rat. The physiology of the cells including the mitoses of fibroblasts was normal. The migration and extension of the various cells were unchanged. The authors stated that "living fibrilloblasts, as they moved about in the cultures, sometimes touched or even migrated over DDT crystals without appreciable injury to themselves during a period of several days." Some observations were carried out for periods as great as 21 days.

In spite of the importance of the nervous system, a detailed review of early literature indicates that although the presence of some specialized nervous function may be necessary for the manifestation of DDT poisoning, the mere occurrence of specialized nervous fibers in certain protozoa or the occurrence of a rather complex nervous system in mollusks is not sufficient to render these forms susceptible. Just as there is no explanation for the effect of DDT in susceptible species, so there is no explanation for the fact that certain species and even entire phyla are inherently resistant to the compound.

A review (Hayes, 1959a) of literature on the effects of DDT on the nervous system reveals that all major parts, both central and peripheral, are affected. Whereas effects on specific portions, notably the cerebellum and the motor cortex, have been viewed as of greatest importance, it probably is more accurate to emphasize the interaction of functions, all modified to some degree.

One sensitive measure of brain activity is the electrocorticogram. Farkas *et al.* (1968) found that the wave frequency showed considerable increase in resting rats that had received 20 mg/kg/day as a result of dietary intake. Rats that had received 5 mg/kg/day did not exhibit this change while at rest, but even these exhibited abnormalities when exposed to a rhythmic light stimulus. Electrical activity may become abnormal only a minute or two after administration of a large dose of DDT; four stages culminating in generalized seizures have been described by Joy (1973). Phenobarbital, but not diphenylhydantoin or trimethadione, was effective in stopping seizures.

The most characteristic effect of DDT in contrast to dieldrin, for example, is the production of tremor. Sufficient dosages of DDT produce tremor even at ambient temperatures that approach body heat. However, dosages of DDT that produce no other clinical effect make rats more sensitive to low temperatures, and this sensitivity may be demonstrated conveniently by having the rats swim to exhaustion in cool water. The ability of a rat to keep afloat is more dependent on coordination than on physical strength.



It was found that normal rats can swim for over 100 min in water 25°C or warmer but for only about 30 min at 23°C and less than 10 min at 15°C. At any given temperature, male rats could swim longer than females. Of the temperatures studied, the effect of DDT was most striking at 25°C; normal females swam for 117 min, whereas those that had received a dietary level of 50 ppm (2.62 mg/kg/day) swam only an average of 7 min. At 27°C, both groups of rats swam over 120 min, and at 37°C the swimming time of rats on a dietary level of 200 ppm approached or equaled that of normal animals. In order to expedite testing, the conditions were standardized at a water temperature of 19.9–20.2°C, and 0.006% sodium lauryl sulfate was added to the water to reduce the trapping of air in the fur, which tends to buoy up rats and permit them to swim longer. Under these conditions, the swimming time of normal animals averaged about 12 min when they were first tested but approached 16 min within a month if the animals were tested repeatedly. If DDT was fed for 2 weeks starting after the rats had become accustomed to swimming, those at a dietary level of 20 ppm showed a reduction in swimming time that was of questionable statistical significance. Those at a dietary level of 50 ppm showed a gradual decrease in swimming time during the 2-week exposure period and failed to return to the endurance of the controls in over a month after dosing was stopped. At dietary levels of 150 and 400 ppm, there was a sharp reduction in swimming time (to 7.3 and 4.0 min, respectively) on the first day of dosing, followed by a gradual decline during the remaining 13 days of dosing and then a slow, incomplete return toward normal (Hayes, 1982).

When measured by the same device 4 min after rats had swum to exhaustion, the tremor of a rat on a dietary level of 200 ppm involved much more energy than that of a normal rat, but the frequencies of the tremors were essentially identical—13–15/sec. In spite of the difference in energy, it appears likely that the tremorigenic action of DDT involves toxicity to that portion of the brain responsible for the control of ordinary shivering. In any event, the presence of tremor depends largely on the temperature of the head. This was demonstrated by Dr. Carl Rothe by placing a rat's head through a hole in a rubber sheet so that the rubber fit snugly about the neck and then varying the temperature of the head and the body relatively independently by separate sprays of either warm or cold water in front of and behind the sheet.

Like tremor, the coldness of the skin and ruffling of the fur seen in acute poisoning probably represent an indication of disturbed thermal regulation. Apparently, it was not until the work of Hrdina *et al.* (1975) that an increase of almost 3°C in body temperature was reported in rats following a fatal (600 mg/kg) oral dosage of DDT.

The central nervous systems of mice and hamsters are equally sensitive, the concentration of DDT in their brains at death being similar. However, after an oral dosage of 500 mg/kg, the DDT concentration of the mouse brain was twice that of the hamster. This cannot be explained by a difference in absorption, metabolism, or excretion but apparently is due to a difference in permeability of the blood–brain barriers of the two species.

When animals received DDT at a dietary level of 205 ppm for 6 weeks, the residues in fat and liver were seven to eight times higher in the mouse, a fact only partially explained by the greater food intake of mice relative to body weight. Although urinary excretion of [<sup>14</sup>C]DDT was similar in previously unexposed hamsters and mice, this excretion was stimulated in the hamster but little affected in the mouse by previous dietary exposure to DDT (Gingell and Wallcave, 1974).

Mice also differ from rats in their hormonal regulation of the basic activity of hepatic microsomal mixed-function enzymes as well as in the response of these enzymes to inducers (Chhabra and Fouts, 1974).

**Cause of Death** Death from DDT poisoning is usually the result of respiratory arrest. The heart continues to beat to the end and in some instances continues a little while after respiration stops. Deichmann *et al.* (1950) found that the onset of hyperirritability was accompanied by an increase in the frequency and amplitude of respiration. Later, with the occurrence of tremors, the depth of respiration frequently returned to a more normal level, but the rate remained high. In some animals respiration stopped suddenly after a deep inspiration during a tonic convulsion. In other animals the rate and amplitude decreased progressively and finally ceased without any terminal spasm. Animals that die of respiratory failure caused by DDT do so after a relatively long period of muscular activity that leaves them exhausted.

It was shown by Philips and Gilman (1946) and Philips *et al.* (1946) that the hearts of dogs given large intravenous doses of DDT were sensitized to epinephrine. This was true not only of injected epinephrine but also of the compound released by the adrenal glands during a seizure. Stimulated in this way, the sensitized hearts of dogs developed an irreversible, fatal ventricular fibrillation. However, the hearts of monkeys were able to recover from fibrillation and resume normal rhythm. It is not clear how important sensitization of the myocardium is when DDT is administered by other routes, but ventricular fibrillation may be the cause of death in animals that die suddenly soon after onset of poisoning.

Thus, DDT not only sensitizes the myocardium in a way similar to that of halogenated hydrocarbon solvents but also, through its action on the central nervous system, produces the stimulus that increases the likelihood of fibrillation.

There is no evidence that repeated, tolerated doses of DDT sensitize the heart. Rats were fed DDT at a dietary level of 200 ppm (about 10 mg/kg/day) for 8 months, during which they received weekly intraperitoneal doses of vasopressin, a compound which causes a temporary myocardial ischemia. Electrocardiograms showed no significant increase in cardiac arrhythmias in the DDT-fed rats compared with controls. Intravenous noradrenaline given at the end of the 8-month period did not produce a greater incidence of arrhythmias in the DDT-fed rats. The same results were obtained in rabbits treated in essentially the same way (Jeyaratnam and Forshaw, 1974).

**Mutation and Carcinogenesis** DDT has been tested in a number of ways for possible mutational effect. Much of this



work has been reviewed in detail together with most of the carcinogenicity studies shown in Table 15.7 (Coulston, 1985). For example, Shirasu *et al.* (1976) listed DDT as a negative chemical in microbial mutagenicity screening studies on 166 pesticides. The test system consisted of rec-assay utilizing H 17 Rec<sup>+</sup> and M 45 Rec<sup>-</sup> strains of *Bacillus subtilis* and reversion assays without metabolic activation using auxotrophic strains of *Escherichia coli* (WP 2) and *Salmonella typhimurium* (Ames series). The further studies with metabolic activation failed to reveal mutagenicity of DDT (Shirasu *et al.*, 1977). McCann *et al.* (1975) and McCann and Ames (1976) reported negative results on DDE in *S. typhimurium* testing with metabolic activation.

At a dosage of 105 mg/kg it produced no increase of dominant lethals in mice (Epstein and Shafner, 1968). However, concentrations of 10 ppm or greater produced chromosome breaks and exchange figures in a marsupial somatic cell line (Palmer *et al.*, 1972). Saturated solutions produced chromosome breaks in the root tips of onion and other plants (Vaarama, 1947). A slight mutagenic effect in mammals has been reported by Markarian (1966). Deletions plus gaps were reported to be more common in the chromosomes of mice that had received DDT. On the whole, *in vitro* tests of the mutagenicity of DDT have given only negative or dubious results (Coulston, 1985).

An unconventional test for mutagenicity involved examination of explants of pulmonary tissue from embryonic mice whose dams had been fed dietary concentrations of 10 and 50 ppm DDT. An increase of diffuse hyperplasia and focal proliferation was observed, but a dosage-response relationship was not clear. Some of the embryos were allowed to live and the experiment was repeated in subsequent generations. There was no continuing progression of the reported changes in succeeding generations (Shabad *et al.*, 1972).

DDT causes inhibition of intercellular communication in cultured rat liver cells (Williams *et al.*, 1981) and in hamster lung fibroblasts (Wärngård *et al.*, 1985, 1987, 1988) like other chlorinated chemicals. The exact significance of the effect is unknown, but it does not seem to involve direct activation of protein kinase C, unlike 12-*o*-tetradecanoylphorbol-13-acetate (Wärngård *et al.*, 1989). *o,p'*-DDT supports the growth of an estrogen-responsive tumor (Robison *et al.*, 1985a).

The question of whether DDT is carcinogenic really seems to be restricted to its action in the liver of some rodents. This matter and its relation to the induction of liver microsomal enzymes by DDT, by other chlorinated hydrocarbon insecticide, and by phenobarbital is discussed in Section 15.2.3.2. Some of the positive findings shown in Table 15.7 have not been found in other studies [National Cancer Institute (NCI), 1978a]. However, there is still the evidence that DDT can act as a promoter of carcinogenesis initiated by aflatoxin and of other chemicals *in vitro* and *in vivo* (Peraino *et al.*, 1975; Schulte-Hermann, 1985; Rojanapo *et al.*, 1987).

**Other Miscellaneous Effects on Organs and Tissues** The effects of DDT and other chlorinated hydrocarbon insecticides on the liver are discussed in Section 15.2.3.2.

Many early reports reviewed by Hayes (1959a) indicate that large doses of DDT may have no effect on the blood or they may produce a moderate leukocytosis and a decrease in hemoglobin, with or without a decrease in the concentration of red cells. The leukocytosis probably is secondary to stimulation of the sympathetic nervous system, while the loss of hemoglobin may be nutritional in origin. Later study has not confirmed the early results. A range of hematologic parameters remained unchanged in squirrel monkeys dosed orally at rates of 0, 0.05, 0.5, 5, and 50 mg/kg/day, even though the highest dosage was fatal within 14 weeks (Cranmer *et al.*, 1972).

Average protein-bound iodine (PBI) levels of 5.42 and 6.93  $\mu\text{g}/\%$ , respectively, were reported in the sera of 42 workers occupationally exposed to chlorinated hydrocarbon insecticides and 51 workers not so exposed. The difference was statistically significant even though all values fell within the normal range of 4–8  $\mu\text{g}/\%$  (Wassermann *et al.*, 1971). It was not recorded whether the workers involved were from the same factory as those with 10 or more years of occupational exposure whose plasma DDT levels were reported by M. Wassermann *et al.* (1970a). The small difference in PBI levels is difficult to evaluate. Goldman (1981) has reported that after a single large dose (100 mg/kg) to rats thyroidal  $^{131}\text{I}$  release was completely inhibited for more than 12 hr. It was the view of Clifford and Weil (1972) that there was no evidence that occupational exposure to DDT has had any effect on human endocrine organs.

The possibility that some pesticides, including DDT, are probiotic has been discussed in Section 2.4.14. Although this general question remains open, one group of investigators has shown clearly that what at first appeared to be an immunological response really involved a quite different, predictable effect. Briefly, it was shown that guinea pigs sensitized to diphtheria toxoid were less susceptible to anaphylaxis in response to a challenge dose of the toxoid if they were pretreated with DDT at a dosage of only 10–20 mg/kg/day. Direct measurement of antitoxin production indicated little or no difference between protected and unprotected animals. Furthermore, some protection was given by DDT administered for only 3 days prior to the induction of anaphylaxis (Gablík *et al.*, 1973, 1975). Further study showed that DDT treatment reduced the histamine levels in the lungs of both immunized and nonimmunized animals. The number of detectable mast cells was also reduced; this was true whether the count was made in tissues from guinea pigs dosed systemically with DDT or in lungs and mesenteries from untreated animals exposed to DDT *in vitro* at concentrations ranging from 10 to 45 ppm. These results indicated that the protection offered by DDT was the result of a reduction of the amount of histamine available for sudden release in response to a challenge dose of toxoid (Askari and Gablík, 1973). Regardless of exposure to DDT, immunization leads to an increase in detectable mast cells (Gablík *et al.*, 1975). DDT has been reported to cause acute renal failure in rats after intravenous infusion (Koschier *et al.*, 1980).

**Effects on Reproduction** It was shown very early (Burlington and Linderman, 1950) that DDT produces a striking inhibition of testicular growth and secondary sexual charac-



teristics of cockerels when injected subcutaneously in dosages as high as 300 mg/kg/day. Changes in the testis involve the tubules and not the interstitial tissues, and they have been attributed to an estrogen-like action of DDT.

It must be noted that the action of DDT on the testis of chickens is dosage related. Before the problem of residues became evident, DDT was used extensively for control of lice and common mites on chickens without any adverse effects on egg production or other aspects of reproduction. Many rats would be killed the first day if they were given the dosage of DDT that has been shown to affect the testis of cockerels. The report that under special conditions DDT has a gonadotoxic effect (Rybakova, 1968) is of questionable significance in view of the results of multigeneration tests in rats, mice, and dogs. Dean *et al.* (1980) were unable to demonstrate any changes in either serum androgens or testicular synthesis of testosterone in young rats after exposure to DDT despite significant induction of metabolism of testosterone by isolated hepatic microsomes.

Intraperitoneal injection of as little as 5 mg/kg of technical DDT or 1 mg/kg of *o,p'*-DDT causes a significant increase in weight of the uterus of normal immature female rats or of ovariectomized adult females. A much smaller stimulation is caused by *p,p'*-DDT. Treatment of rats with DDT, especially *o,p'*-DDT, 2 hr before injection of [6,7-<sup>3</sup>H] estradiol-17 inhibited uptake of the hormone by the uterus *in vivo*, possibly by competition for binding sites. Isomers of DDD and DDE do not influence uterine weight or the binding of estradiol (Welch *et al.*, 1969). It seems unlikely that metabolic activation of *o,p'*-DDT is necessary as is true of *o,p'*-methoxychlor (Kupfer and Bulger, 1979). The action of *o,p'*-DDT on the uterus seems to be as a long-acting agonistic estrogen interacting with the same receptor as 17 $\beta$ -estradiol and causing the formation of the so-called induced protein (Ireland *et al.*, 1980; Robison *et al.*, 1984; Galand *et al.*, 1987). However, some differences from estradiol have been recorded (Robison *et al.*, 1985b). The lesser enantiomer of *o,p'*-DDT seems to be the active isomer (McBlain, 1987). The binding and estrogenic activity of DDT analogs in rats is only about 1/10,000 as great as that of diethylstilbestrol (Nelson, 1973).

A considerably smaller dosage of *o,p'*-DDT resulting from a dietary level of 10 ppm for 2–9 months had no effect on reproduction in ewes (Wrenn *et al.*, 1971b). In a similar way, dietary levels of *o,p'*-DDT as high as 40 ppm, giving a dosage level of about 2.1 mg/kg/day in rats, failed to interfere with reproduction and lactation in these animals, although dosage was continued through two pregnancies (Wrenn *et al.*, 1971a).

The report (Heinricks *et al.*, 1971) that *o,p'*-DDT significantly advances puberty, induces persistent vaginal estrus after a period of normal estrous cycles, and causes other reproductive abnormalities in female rats would at first appear inconsistent with the lack of effect of technical DDT or of *o,p'*-DDT on reproduction cited above. The same is true of other effects of *o,p'*-DDT demonstrated by the same investigators (Gellert *et al.*, 1972). The abnormal effects were obtained initially by injecting 1 mg of the *o,p'*-DDT subcutaneously on the second, third, and fourth days of life (counting the day of birth as zero). Because rat pups on the third day weight about 12 gm or less

each, it follows that the subcutaneous dosage was about 83.3 mg/kg/day or more, that is, about 40 times greater than the highest oral dosage of *o,p'*-isomer fed to breeding rats and about 10<sup>5</sup> times greater than what ordinary people get in their food.

Ottoboni (1969) found that female rats reproduced normally when fed DDT for two generations at dietary levels as high as 200 ppm (about 10 mg/kg/day except during lactation, when intake is increased about threefold). In fact, at a dietary level of 20 ppm, the dams had a significantly longer reproductive life span (14.55 months) than their littermate controls (8.91 months); the number of females becoming pregnant after the age of 17 months and the number of successful pregnancies after that age were significantly different in the two groups (Ottoboni, 1972).

In a study focused mainly on DDT in milk, the full ability of rats to reproduce at a dietary level of 200 ppm was confirmed, and the ability of dams injected intraperitoneally at levels as high as 100 mg/kg/day to rear their young was demonstrated (Hayes, 1976b).

A six-generation test of reproduction in mice showed no effect of DDT at a dietary level of 25 ppm on fertility, gestation, viability, lactation, and survival. A level of 100 ppm produced a slight reduction in lactation and survival in some generations but not all, and the effect was not progressive. A level of 250 ppm was distinctly injurious to reproduction (Keplinger *et al.*, 1970). The dietary concentrations used determine dosages of 3.33, 13.3, and 33.2 mg/kg/day in nonpregnant, nonlactating, adult, female mice. The intake is much higher in both young and lactating mice. The authors concluded that their study provided no obvious reason for continuing reproduction tests for more than three generations.

Four female dogs of unstated age that previously had received DDT at the rate of 12 mg/kg/day, 5 days/week, for 14 months were bred when they went into heat. The males involved had been fed aldrin (0.15 mg/kg/day) plus DDT (60 mg/kg/day) for 14 months prior to breeding but not during breeding. Two of the females went into heat but failed to become pregnant, and one failed to come into heat during 12 months after feeding stopped. Four of six pups born to the fourth female died within 1 week of birth; the other two were weaned successfully even though only two posterior mammae of the mother were functional (Deichmann *et al.*, 1971b). A three-generation study failed to confirm any of the injuries suggested by the study of four dogs. In the three-generation study, male and female dogs were fed technical DDT from weaning at rates of 0, 1, 5, and 10 mg/kg/day. Observations were made on 135 adult females, 63 adult males, and 650 pups. There were no statistically significant differences among controls and DDT-treated dogs in length of gestation, fertility, success of pregnancy, litter size, or lactation ability of the dams; in viability at birth, survival to weaning, sex distribution, and growth of pups; or in morbidity, mortality, organ/body weight ratios, or gross histological abnormalities in all the animals studied. The only clear difference was that DDT-treated females had their first estrus 2 or 3 months earlier than the control dogs. There was a slight increase in liver/body weight ratio in some DDT-treated animals but the difference was not statistically significant, not



dosage-related, and not associated with any histological change (Ottoboni *et al.*, 1977).

When *p,p'*-DDT was administered to pregnant mice at a rate of 1 mg/kg on days 10, 12, and 17 of gestation, it was not teratogenic but did alter the gonads and decrease the fertility of the young, especially the females (McLachlan and Dixon, 1972). A single dose at the rate of 15 mg/kg or repeated doses of 2.5 mg/kg/day given during pregnancy may be embryotoxic but not teratogenic to mice (Schmidt, 1973). Why one or a few doses during pregnancy may be embryotoxic although the same dosage is harmless when administered during the entire reproductive period is of theoretical but no practical importance.

Teratogenic effects of DDT have not been seen in studies of reproduction, including those for two generations in rats, six generations in mice, and three generations in dogs.

Because of the estrogenic properties of large doses of DDT, the compound was considered as a possible cause of abortion in dairy cattle, but no evidence for a relationship was found (Macklin and Ribelin, 1971). A similar conclusion was reached regarding human abortions (O'Leary *et al.*, 1970).

**Behavioral Effects** Behavioral changes may be demonstrated in animals receiving DDT daily at rates too low to produce illness. Khairy (1959) was able to detect ataxia in the form of changes in gait in rats that had been fed DDT at dietary levels of 100 ppm or more for 21 days. The results were recorded in terms of the tangent, that is, the ratio of the width and length of step. At a dosage of about 5 mg/kg/day the ratio was less than normal, a change attributed to an exaggeration of the stretch reflex. At dosages of about 10, 20, and 30 mg/kg/day, the ratio was progressively increased above normal as a result of broadening of the gait and shortening of the steps. These same dosage levels did not affect problem-solving behavior or speed of locomotion. The experimental animals were found to be generally less reactive to stress than normal ones. The acoustic startle response of rats is significantly increased after a 12.5 mg/kg dose of *p,p'*-DDT but can be attenuated by phenytoin and an adrenergic receptor antagonist, phenoxybenzamine (Tilson *et al.*, 1985, 1986; Saitoh *et al.*, 1986; Herr *et al.*, 1987), which also decreased DDT-induced myoclonus (Huang and van Voert, 1978). See also Effects on the Nervous System.

**Pathology** Morphological changes are inadequate to account for death from DDT poisoning. Changes that occur in the liver are discussed in Section 15.2.3.2. Mild to moderate morphological changes have been reported in the kidneys of animals that had received massive single doses or repeated doses; examples are fatty degeneration, necrosis, and calcification (Lillie *et al.*, 1947; Stohlman and Lillie, 1948) or slight brown pigmentation of the convoluted tubular epithelium (Fitzhugh and Nelson, 1947). However, it sometimes has happened that a complete absence of change in the kidney has been reported in connection with other studies carried out in the same laboratories (Lillie and Smith, 1944; Nelson *et al.*, 1944).

**Treatment of Poisoning in Animals** The more successful studies of treatment of animals poisoned by DDT involve the nervous system. Smith and Stohlman (1944) noted the possibility that narcotics in general may exhibit an antagonism to DDT. Rats survived on a diet containing 1000 ppm DDT for 90 days when they received cyclohexanone in the same diet at the rate of 2000 ppm but were uniformly killed in a shorter period when they received DDT at the same rate but without cyclohexanone. Later, it was shown that cyclohexanone offers no protection when used as a solvent for single massive doses of DDT (Deichmann *et al.*, 1950).

Smith and Stohlman (1945) later showed that, when rats were given urethane and, to a lesser extent, sodium dilantin as required after the onset of illness, the animals were protected from poisoning. Sodium amobarbital gave slight benefit, sodium phenobarbital a doubtful benefit, and paraldehyde no protection at all. All drugs were given intraperitoneally except paraldehyde, which was given by stomach tube. The mortality of rats treated with urethane was 12.5% and that of their controls was 80%. A total dosage of 1.2–2.5 gm/kg spread over a period of 1–3 days was found most satisfactory. Sodium dilantin reduced mortality to 46.7%, compared to 96.7% for the controls. The smallest effective dosage was 200–250 mg/kg, a value very close to the LD 50, which, under the conditions of the test, was 300 mg/kg.

Läuger *et al.* (1945a,b) also found that sodium phenobarbital was of questionable value in treating rats poisoned by DDT. However, completely different results were seen in larger animals. Philips and Gilman (1946) found phenobarbital by far the most outstanding remedy they tested. In a dosage well below the anesthetic level, it not only prevented death in many instances but also controlled tremor and convulsions. Signs of illness were more readily controlled in dogs and cats than in monkeys, which required nearly a full anesthetic dosage before tremors completely disappeared.

Magnesium sulfate did not reduce mortality in poisoned dogs and cats, although it did control tremors and convulsions briefly. Sodium bromide was entirely ineffective. Mortality was reduced with urethane, but a full anesthetic dosage was required to control tremor and convulsion. Similarly, sodium barbital and sodium pentobarbital controlled symptoms only when given in full anesthetic doses and even then did not greatly reduce mortality. 5,5-Diphenylhydantoin (phenytoin), when given to rats before they received DDT, reduced the lethal action without showing a notable effect on the signs of poisoning; it was not effective in cats. More recently, Tilson *et al.* (1985, 1986) have reported that phenytoin attenuates the tremor produced in rats by DDT and permethrin but not by lindane and chlordecone.

Vaz and his colleagues (1945) were apparently the first to note the antidotal effect of calcium in DDT poisoning. Dogs were given DDT orally as a 10% oily solution at a daily dosage of 100 mg/kg until signs of intoxication appeared. The same dosage could then be repeated to produce intense symptomatology from which the animals would recover spontaneously in 12–24 hr. For the actual tests, a larger challenge



dosage of DDT (150–200 mg/kg) was used. Each dose of calcium gluconate (30 ml of a 10% solution) was injected intravenously into dogs weighing 8–18 kg. Dogs that were injected with calcium gluconate daily for 4 days and challenged with a large dose of DDT on the fourth day developed no symptoms or only slight ones. Dogs receiving a single dose of calcium gluconate showed symptoms of short duration and survived following a dosage of DDT large enough to kill two controls.

Koster (1947) studied cats poisoned by the intravenous injection of a soya lecithin–corn oil emulsion of DDT. A comparison was made of several aspects of intoxication, including number of convulsions, general severity (tremors, prostration, dyspnea), duration, and mortality. Both calcium gluconate and sodium gluconate reduced mortality but not severity. Gluconic acid increased the survival time, reduced mortality, but did not reduce convulsions or severity. Calcium chloride reduced convulsions but not mortality or tremors. Molecular equivalent doses of the candidate antidotes were used. Gluconic acid and its two salts were effective against an LD 95 dosage of DDT. The lifesaving capacity of calcium gluconate at a rate of 40 mg/kg was confirmed by Judah (1949), even though he found normal blood calcium values in most poisoned but unmedicated animals. One animal showed a high calcium value, and Cameron and Burgess (1945) reported a similar result. It has been suggested that increased blood calcium may be associated with acidosis caused by the accumulation of lactate.

Calcium has, then, an antidotal action against DDT in intact animals of several species. The suppression by calcium of the effect of DDT on the isolated nerve and muscle of the rat has been demonstrated (Eyzaguirre and Lilienthal, 1949). The hypothesis has been advanced (Welsh and Gordon, 1946; Gordon and Welsh, 1948) that certain neurotoxins, including DDT, act by delaying the restoration of calcium ions to a surface complex following breaking of the chelate linkage of calcium ions to surface polar groups by an initial exciting impulse. This action of the neurotoxin is conceived as depending largely on its physical rather than on its chemical properties. The hypothesis is helpful in explaining the fact that a wide variety of chemically unrelated compounds produce repetitive responses in excitable tissue and also the fact that many compounds that show a high toxicity for arthropods and mammals are fat-soluble and chemically relatively inert. It has been pointed out that this hypothesis postulates a very localized action of calcium at the nerve cell membrane; the hypothesis is not inconsistent with the finding that the blood calcium of poisoned animals may be unchanged or even increased. On the other hand, calcium may help to offset the effects of DDT on calcium-dependent ATPases, especially in the neuronal axons (see Biochemical Effects, p. 755).

Having observed the effect of DDT on the metabolism of glucose and glycogen, Luger and his colleagues (1945a,b) investigated the use of glucose as an antidote. All of the 10 dogs given 2000 mg of DDT per kilogram of body weight orally in the form of an oil solution died within 8–24 hr. Five of the 10 dogs treated with one or more 20-ml doses of 20%

glucose survived the same dosage of DDT. The glucose was given intravenously in most instances.

Koster (1947) found that glucose given before or after an LD 33 dosage reduced convulsions and mortality and, when given before the poison, reduced tremors, prostration, and dyspnea in cats. Glucose, unlike gluconic acid and its sodium and calcium salts, was ineffective against an LD 95 dosage except to increase the time of survival. Insulin given intramuscularly 16–25 min before DDT increased the survival time and the severity of poisoning but did not affect mortality or convulsions. When given 53–130 min before DDT, insulin reduced convulsions in animals that died but increased convulsions, tremors, and other disorders in the survivors.

### 15.3.1.3 Toxicity to Humans

**Experimental Oral Exposure** Table 15.8 summarizes the effects of one or a few carefully measured oral doses of DDT. The results are consistent with those in accidents reported by Garrett (1947) and Hsieh (1954) in which it was possible to

**Table 15.8**  
Summary of the Effects of One or a Few Oral Doses of DDT on Volunteers

| Dose (mg) and formulation | Result   | Reference                 |
|---------------------------|--|---------------------------|
| 250 × 9, suspension       | no effect  | Domenjoz (1944)           |
| 1500, butter solution     | no effect, but mice killed when fed 6 and 12 hr after dose   | MacCormack (1945)         |
| 500, oil solution         | no clinical effect   | Neal <i>et al.</i> (1946) |
| 770, oil solution         | no clinical effect; DDA measured in urine  | Neal <i>et al.</i> (1946) |
| 250, suspension           | none except slight disturbance of sensitivity of mouth   | Velbinger (1947a,b)       |
| 250, oil solution         | variable hyperesthesia of mouth  | Velbinger (1947a,b)       |
| 500, oil solution         | variable hyperesthesia of mouth  | Velbinger (1947a,b)       |
| 750, oil solution         | disturbance of sensitivity of lower part of face; uncertain gait; peak reaction (6 hr after ingestion) characterized by malaise, cold moist skin, and hypersensitivity to contact; reflexes normal   | Velbinger (1947a,b)       |
| 1000, oil solution        | same as above; no joint pains, fatigue, fear or difficulty in seeing or hearing  | Velbinger (1947a,b)       |
| 1500, oil solution        | prickling of tongue and around mouth and nose beginning 2.5 hr after dose; disturbance of equilibrium; dizziness; confusion; tremor of extremities; peak reaction (10 hr after ingestion) characterized by great malaise, headache, and fatigue; delayed vomiting; almost complete recovery in 24 hr | Velbinger (1947a,b)       |



estimate accurately the amount ingested. It may be concluded that a single dose at the rate of 10 mg/kg produces illness in some but not all subjects even though no vomiting occurs. Smaller doses generally produce no illness, although a dosage of 6 mg/kg produced perspiration, headache, and nausea in a man who was sickly and who was hungry at the time of eating. Persons who were made sick by 10 mg/kg have not shown convulsions, but convulsions have occurred in accidents when the dosage level was 16 mg/kg or greater (Hsieh, 1954). Rarely, a dosage as high as 20 mg/kg may be taken without apparent effect (MacCormack, 1945). Dosages at least as high as 285 mg/kg have been taken accidentally without fatal result (Garrett, 1947). However, large doses lead to prompt vomiting, so the amount actually retained cannot be determined accurately.

In acute poisoning a slight decrease in hemoglobin and a moderate leukocytosis without any constant deviation in the differential white count have been observed in volunteers (Velbinger, 1947a,b). These findings are considered secondary to the neurological effects.

It has been noted in the course of tests with volunteers that dilute colloidal aqueous suspensions of DDT are odorless and tasteless (Domenjot, 1944; Hoffman and Lendle, 1948). Saturated alcoholic solutions of DDT have a weak aromatic taste, or rather odor. Some people find these solutions slightly anesthetic to the tongue (Hoffman and Lendle, 1948). The taste of DDT in vegetable oil is so slight that many persons cannot identify capsules containing 0, 3.5, and 35 mg of DDT when they are presented separately but can arrange them in proper order when one of each is available for comparison.

The possible clinical effects of many repeated doses of DDT were first explored by Fennah (1945). Because of his interest in predicting the results of indiscriminate use, he expressed the exposures in terms of environmental levels rather than in dosage units. The exposures were clearly higher than those ordinarily encountered. In one test, lasting a total of 11.5 months, Fennah daily inhaled 100 mg of pure DDT and drank water dusted at the rate of 3240 mg/m<sup>2</sup>. Much of the inhaled dust must have been deposited in the upper respiratory tract and swallowed. Later, for 1 month Fennah ate food all of which had been sprayed at the rate of 2160 mg/m<sup>2</sup> after it had been served. No ill effect of any kind was observed.

Some later studies of DDT in volunteers have been designed to explore the details of storage and excretion of the compounds in humans and to search for possible effects of doses considered to be safe. In the first of these studies, men were given 0, 3.5, and 35 mg/person/day. These administered dosages plus DDT measured in the men's food resulted in dosage levels of 0.0021–0.0034, 0.038–0.063, and 0.36–0.61 mg/kg/day, respectively, the exact value depending on the weight of each individual. Six volunteers received the highest dosage of technical DDT for 12 months, and three received it for 18 months. A smaller number of men ingested the lower dosage of technical DDT or one of the dosages of *p,p'*-DDT for 12–18 months. No volunteer complained of any symptom or showed by the tests any signs of illness that did not have an easily

recognizable cause clearly unrelated to the exposure of DDT. At intervals, the men were given a systems review, physical examination, and a variety of laboratory tests. Particular attention was given to the neurological examination and liver function tests, because the major effects of DDT in animals involve the nervous system and the liver (Hayes *et al.*, 1956).

The same result was obtained in a second study in which the same dosages were given for 21 months and the volunteers were observed for a minimum of 27 additional months (Hayes *et al.*, 1971).

In the first study, the storage of DDT was proportional to dosage, but there was a then unexplained difference in the storage of the *p,p'*-isomer and of technical DDT. Following dosing for 12 months, the pure material was stored in fat at an average concentration of 340 ppm, but the technical material was stored at an average of only 234 ppm. The difference was statistically significant for the 3.5 mg/person/day dosages given for 3–6 and for 7–18 months. The difference was significant for the 35 mg/person/day doses after 7–18 months of dosing but not after only 3–6 months.

Men who ate *p,p'*-DDT showed a definite increase in the absolute amount of DDE stored. After 6 months at a dosage of 35 mg/person/day, eight men showed an average DDE fat storage of  $32.6 \pm 7.0$  ppm as compared to  $12.3 \pm 1.5$  ppm for the same individuals upon entering the investigation. There was a further increase of DDE storage as exposure progressed. However, DDT was stored in so much greater concentration that the relative storage of DDE decreased sharply. Thus, after 6 months at a dosage of 35 mg/person/day, eight men stored only 14% of their total DDT-derived material in the form of DDE as compared to 65% for the same persons at the beginning of the investigation.

The storage of DDE by men who ate technical DDT presented a different picture. Until 18 months after exposure, there was no clear evidence that these men stored any more DDE after exposure than they did before. However, at 18 months the only three samples available showed DDE concentrations ranging from 28 to 85 ppm, all substantially above general population levels. Thus, both the total amount stored and the rate at which DDT converted to DDE served to distinguish the metabolism of *p,p'*-DDT and technical DDT in humans (Hayes *et al.*, 1956). This was true even though later study showed that the concentration of DDE in serum increased immediately in persons ingesting technical DDT at rates of 10 and 20 mg/person/day. Of course, daily values were subject to considerable variation, but the upward slopes of the graphs recording the results were apparent in 60 days or less and apparently the graphs were straight throughout the 5-month feeding period. Under the same conditions, the level of DDT in serum increased within 1 day and continued to increase in a curvilinear fashion for 5 months (Apple *et al.*, 1970). A similar rapid increase reaching its maximum in 30 hr after a single exposure has been observed in workers (Edmundson *et al.*, 1969a). The more rapid excretion of *o,p'*-DDT was demonstrated by Morgan and Roan (1972). In a second study in which the volunteers received 0, 3.5, and 35 mg/person/day, the storage of DDT was again propor-



**Table 15.9**  
Storage of DDT in Volunteers

| Type of DDT    | Added dosage<br>(mg/person/day) | Concentration of DDT <sup>a</sup>                      |              |   |              | Significance<br>of difference<br>( <i>p</i> ) |
|----------------|---------------------------------|--|--------------|---|--------------|---|
|                |                                 | First study <sup>b</sup><br>11 months or more<br>(ppm) |              | Second study <sup>c</sup><br>21.5 months<br>(ppm) |              |   |
| Technical      | 0                               | 8–17   | (12.5 ± 4.5) | 16–30   | (22.0 ± 2.9) | >0.1  |
|                | 3.5                             | 26–33  | (23.8 ± 1.4) | 59–76   | (50.2 ± 5.6) | <0.025  |
|                | 35                              | 101–367  | (234 ± 21.4) | 105–619   | (281 ± 79.5) | >0.4  |
| Recrystallized | 35                              | 216–466  | (340 ± 36.4) | 129–659   | (325 ± 62.2) | >0.2  |

<sup>a</sup> Range, mean ± SEM.

<sup>b</sup> Hayes *et al.* (1956).

<sup>c</sup> Hayes *et al.* (1971).

tional to dosage. Although, in this instance also, the storage of technical DDT was less than that of *p,p'*-DDT, the difference was not statistically significant. The real but very gradual accumulation of DDE was confirmed. A steady state of storage was approached later in the second study (18.8–21.5 months) than in the earlier one (about 12 months). The second study was superior in that more men were observed for a longer period but inferior in that dosing was less regular. Because of the latter difficulty, it seems impossible to decide whether 12 months or 21.5 months is a more valid estimate of the time necessary for people to approach a steady state of storage when intake is uninterrupted and unvarying in amount. It is interesting that the storage levels eventually reached at the same dosage in the two studies were statistically indistinguishable in most instances (see Table 15.9). In the one instance in which a statistical difference existed, the greater storage by men in the second study may have been explained by the fact that some of them inadvertently received higher doses than intended.

DDT was lost slowly from storage in fat after dosing was stopped. The concentration remaining following 25.5 months of recovery was from 32 to 35% of the maximum stored for those who had received 35 mg/person/day but was 66% for those who had received only 3.5 mg/person/day, indicating slower loss at lower storage levels (Hayes *et al.*, 1971).

Morgan and Roan (1971) fed volunteers not only technical DDT but also *p,p'*-DDE and *p,p'*-DDD. They found that DDE is stored more tenaciously than the other compounds in humans, the order being *p,p'*-DDE > *p,p'*-DDT > *o,p'*-DDT ≥ *p,p'*-DDD. The slow metabolism of DDT to DDE was confirmed. It was noted that *p,p'*%-DDT is lost from storage in adipose tissue much more slowly in humans than in the monkey, dog, or rat.

Less than 18% *p,p'*-DDT and *p,p'*-DDE is carried in human erythrocytes. In plasma of ordinary fat content, less than 1% of all DDT-related compounds is carried by the chylomicrons. Instead, these compounds are carried by proteins and are undetectable in plasma from which protein has been precipitated. Following ultracentrifugation, *p,p'*-DDT and *p,p'*-DDE are found mainly in the triglyceride-rich, low-density and very low-density lipoproteins. Following continuous electrophore-

sis, these compounds are found mainly in association with plasma albumin and α-globulins (Morgan *et al.*, 1972).

DDA is the main urinary metabolite of DDT. In humans, it was found first in a volunteer by Neal *et al.* (1946), who reported that, following ingestion of 770 mg of *p,p'*-DDT, excretion rose sharply to 4.0 mg/day during the second 24-hr period, decreased rapidly on the third and fourth days, decreased gradually thereafter, but was still above baseline on day 14. Judging from a graph, the highest concentration was about 2.6 ppm.

Much later studies in volunteers who received smaller but repeated doses confirmed the very rapid rise in excretion of DDA (Roan *et al.*, 1971; Hayes *et al.*, 1971) and showed that a steady state of excretion was reached after about 6–8 months. During a 56-week period of continued dosing after equilibrium was fully established, the concentration of DDA associated with technical DDT at the rate of 35 mg/person/day varied from 0.18 to 9.21 ppm and averaged 2.98 ppm; corresponding values for *p,p'*-DDT were 0.40–6.27 ppm with a mean of 1.88 ppm. Thus technical DDT, as compared to *p,p'*-DDT, was excreted more effectively and stored less.

During the latter half of the dosing period, it was possible in the two groups receiving recrystallized and technical DDT at the rate of 35 mg/person/day to account for an average of 13 and 16%, respectively, of the daily dose in terms of urinary DDA. The excretion of DDA was relatively constant in each individual, but marked differences were observed between men receiving the same dose. For example, over the period of 56 weeks the highest rate measured for one man was 0.16 mg/hr while the lowest rate for another in the same group was 0.15 mg/hr. Their mean rates during this period were 0.089 and 0.269 mg/hr, respectively. The difference was highly significant ( $P < 0.001$ ) (Hayes *et al.*, 1971).

**Experimental Dermal Exposure** Depending on dosage, oral administration of DDT to volunteers has produced either no illness or brief poisoning entirely similar to that seen in experimental animals. The oral dosage necessary to produce any clinical effect was almost always 10 mg/kg or more. It is a strange coincidence that, in two studies involving only three



subjects in all, experimental dermal exposure to DDT was followed by fatigue, aching of the limbs, anxiety or irritability, and other subjective complaints. Recovery was delayed a month or more (Wigglesworth, 1945; Case, 1945). In neither study was there an independent control. Although the dosage was unmeasured, the amounts of DDT absorbed must have been much smaller than those involved in the oral tests. One of the studies involved self-experimentation by one man. A similar but somewhat more severe test on six volunteers produced no toxic or irritant effect at all (Dangerfield, 1946). In view of all other experiments and extensive practical experience, it must be concluded that the illnesses reported by Wigglesworth and Case were unrelated to DDT.

With the exceptions just mentioned, dermal exposure to DDT has been associated with no illness and usually no irritation (Domenjoz, 1944; Cameron and Burgess, 1945; Dangerfield, 1946; Chin and T'Ant, 1946; Wasicky and Unti, 1944; Draize *et al.*, 1944; Haag *et al.*, 1948; Fennah, 1945). In fact, Hoffman and Lendle (1948) reported that even subcutaneous injection of colloidal suspensions of DDT in saline in concentrations up to 30 ppm caused no irritation. Zein-el-Dine (1946) reported that DDT-impregnated clothing caused a slight, transient dermatitis, but the method of impregnation was not stated and the absence of solvent was not guaranteed. Other more thorough studies of DDT-impregnated clothing have found it nonirritating (Domenjoz, 1944; Cameron and Burgess, 1945).

Chin and T'Ant (1946) applied small pads impregnated with different formulations of DDT to the inner surface of the forearm of 32 volunteers whose cutaneous sensation had previously been measured for a period of 5 weeks. Pads impregnated with all the elements of the formulation except DDT were applied to the corresponding position on the other arm as a control. Powdered DDT and 5% solutions of DDT showed little effect. Ten percent and 20% solutions in olive oil and petroleum showed no remarkable effect on sensation of pain, cold, or heat but reduced tactile sensation in most cases so that the minimal pressure that could arouse this sensation was 1–2.5 gm/cm<sup>2</sup> higher than in the control.

**Experimental Respiratory Exposure** Neal *et al.* (1944) reported almost continuous daily exposure to aerosols sufficient to leave a white deposit of DDT on the nasal vibrissae of the volunteers. This exposure produced moderate irritation of the nose, throat, and eyes. Except for this irritation during exposure, there were no symptoms, and laboratory tests and physical examination, including neurological evaluation, failed to reveal any significant changes. The studies by Fennah (1945) that involved both respiratory and oral exposure produced no detectable ill effect, as discussed above. Stammers and Whitfield (1947) reported tests in which volunteers were exposed to DDT dispersed into the air either by volatilizing units or by continuously or intermittently operated aerosol dispensers. In some instances, a slight odor and some dryness of the throat were noticed, but otherwise the results were negative.

**Therapeutic Use** The use of DDT for treating human body lice, head lice, and scabies has been reviewed by Simmons (1959). Obviously, these uses offered a possibility of dermal absorption, but such absorption of dry DDT is very limited. Persons who had DDT blown into their clothing as they wore it must have inhaled some of the compound, and this was especially true of persons who used hand or power equipment to apply the dust to hundreds of people per day in mass delousing stations set up to control typhus. However, the dosages absorbed cannot have been so large as in some instances in which DDT has been administered by mouth. Even smaller absorbed dosages for the general population were involved in the use of DDT for the control of other vector-borne diseases, especially malaria. These facts must not lead us to forget the tremendous contribution that DDT has made to human health through control of the vectors of typhus, malaria, plague, and several lesser diseases (Spindler, 1983; Coulston, 1985).

DDT has been used on an experimental basis at oral dosage rates varying from 0.3 to 3 mg/kg/day for periods up to 7 months in an attempt to decrease serum bilirubin levels in selected patients with jaundice. No side effects were observed. No improvement was noted in patients with jaundice based on cirrhosis who had no demonstrated liver enzyme deficiency. However, in a patient with familial, nonhemolytic, unconjugated jaundice based on a deficiency of glucuronyltransferase, treatment with DDT rapidly reduced the plasma bilirubin level to the normal range and relieved the patient of nausea and malaise from which he had suffered intermittently. The liver function tests as well as other laboratory findings remained normal. The improvement was maintained during the 6 months when DDT was administered and had persisted for 7 additional months at the time the report was written. In this case, a dosage of 1.5 mg/kg/day produced a steady rise in plasma levels of *p,p'*-DDT from an initial level of 0.005 ppm to a maximum of 1.33 ppm at the end of treatment. At this time, the concentration in body fat was 203 ppm. Plasma levels fell slowly after dosing was stopped (Thompson *et al.*, 1969). The highest daily intake in this series was six times greater than the highest level administered in earlier studies of volunteers and about 7500 times greater than the DDT intake of the general population. The highest value for *p,p'*-DDT in serum observed in the entire series was 1.330 ppm, compared to 0.996 ppm, the highest value reported by Laws *et al.* (1967) for formulation-plant workers. A lesser induction of the microsomal enzymes has been observed in workers also (Kolmodin *et al.*, 1969; Poland *et al.*, 1970).

Rappolt (1970) used a single dose of 5000 mg of DDT to promote the metabolism of phenobarbital, of which his three patients had taken an overdose. The treatment appeared useful. Neither Rappolt nor Thompson encountered any side effects of DDT. However, in addition to whatever action it may have had in promoting the metabolism of phenobarbital, the DDT administered by Rappolt must have acted largely as a pharmaceutical antidote for the barbiturate. The largest dose previously administered intentionally was 1500 mg, which caused



moderate poisoning in a volunteer, who, of course, had received no barbiturate (see Table 15.8).

**Accidental and Intentional Poisoning** The earliest symptom of poisoning by DDT is hyperesthesia of the mouth and lower part of the face. This is followed by paresthesia of the same area and of the tongue and then by dizziness, an objective disturbance of equilibrium, paresthesia and tremor of the extremities, confusion, malaise, headache, fatigue, and delayed vomiting. The vomiting is probably of central origin and not due to local irritation. Convulsions occur only in severe poisoning.

Onset may be as soon as 30 min after ingestion of a large dose or as late as 6 hr after smaller but still toxic doses. Recovery from mild poisoning usually is essentially complete in 24 hr, but recovery from severe poisoning requires several days. In two instances, there was some residual weakness and ataxia of the hands 5 weeks after ingestion.

Involvement of the liver has been mentioned in only a small proportion of cases of accidental poisoning by DDT. In three men who ate pancakes made with DDT and who ingested 5000–6000 mg each, slight jaundice appeared after 4–5 days and lasted 3–4 days (Naevested, 1947). Hepatic involvement and convulsions were reported in an unsuccessful attempt at suicide by ingesting DDT and lindane (Eskenasy, 1972).

Cases of individual and suicidal poisoning in which effects were clearly caused by DDT are summarized in Table 15.10. All of these cases involved ingestion. The signs and symptoms of poisoning were entirely consistent with those observed in volunteers, except that the spectrum of effects was broader because some of the accidental and suicidal doses were very high. A few persons apparently have been killed by uncomplicated DDT poisoning, but none of these cases was reported in detail. Death has been caused much more frequently by the ingestion of solutions of DDT, but in most of these instances the signs and symptoms were predominantly or exclusively those of poisoning by the solvent (Hayes, 1959a). This does not mean that the toxicity of the solvent always predominates. For example, the recurrent convulsions in a case reported by Cunningham and Hill (1952), though more characteristic of poisoning by one of the cyclodienes, was certainly not typical of solvent poisoning. A 2-year-old child drank an unknown quantity of fly spray of which 5% was DDT, but the nature of the other active ingredients or the solvent was unknown. About 1 hr after taking the material, the child became unconscious and had a generalized, sustained convulsion. Convulsions were present when the child was hospitalized 2 hr after taking the poison, but the fits were controlled by barbiturates and other sedatives. Convulsions reoccurred on day 4 and again on day 21 but were stopped each time following renewal of treatment. On day 12, it was noted that the patient was deaf. Hearing began to improve about day 24 and was normal, as were other neurological and psychic findings, when the patient was seen about 2.5 months after the accident.

Clinical effects of one toxicant may be modified by

**Table 15.10**

Summary of the Effects of the Accidental or Suicidal Ingestion of DDT

| Individual dose (mg), formulation, and number of persons | Results and reference   |
|--|---|
| 300–4500, in food, 1 man                                 | onset in 1 hr; vomiting; restlessness; headache; heart weak and slow; recovery next day (Muhlens, 1946)   |
| Unknown dose, in tarts, 25 men                           | onset in 2–2.5 hr; all weak and giddy; 4 vomited; 2 hospitalized; 1 confused, incoordinated, weak; one with palpitations and numbness of hands; recovery in 24–48 hr (Mackerras and West, 1946)   |
| 5000–6000, in pancakes, 3 men                            | onset 2–3 hr; throbbing headache; dizziness; incoordination; paresthesias of extremities; urge to defecate; wide, nonreacting pupils; reduced vision; dysarthria; facial weakness; tremor; ataxic gait; reduced sensitivity to touch; reduced reflexes; positive Romberg; slightly low blood pressure and persistent irregular heart action; partial recovery in 2–3 days, but slight jaundice appeared 4–5 days after ingestion and lasted 3–4 days; all normal 19 days after poisoning except irregular heart action in one (Naevested, 1947) |
| 2000, in pancakes, 2 men                                 | no illness (Naevested, 1947)  |
| Up to 20,000, in bread, 28 men                           | onset in 30–60 min in those most severely affected; men first seen 2–3 hr after ingestion; in spite of severe early vomiting that reduced the effective dose, severity of illness and especially intensity of numbness and paralysis of extremities proportional to amount of DDT ingested; all but 8 men recovered in 48 hr; 5 others fully recovered in 2 weeks, but 3 men still had some weakness and ataxia of their hands 5 weeks after ingestion (Garrett, 1947, 1950)  |
| Unknown dose, in flour, about 100 women                  | onset about 3.5 hr after ingestion; total of about 85 cases of which 37 were hospitalized; symptoms mild and similar to those in earlier outbreaks except gastrointestinal disturbance in most severe cases included abdominal pain and diarrhea as well as nausea; most fully recovered in 24 hr (Jude and Girard, 1949)   |
| Unknown dose, 14 cases                                   | symptoms in established cases similar to those reported earlier (Francone <i>et al.</i> , 1952)   |
| 286–1716, in meatballs, 8 cases, 11 exposed              | with the exception of one man who was already sick when he received a dosage of 6 mg/kg, poisoning did not occur at dosages of 5.1–10.3 mg/kg. Ingestion of 16.3–120.5 mg/kg produced excessive perspiration, nausea, vomiting, convulsions, headache, increased salivation, tremors, tachycardia, and cyanosis of the lips. Onset varied from 2 to 6 hr, depending on dosage. Recovery required as much as 2 days (Hsieh, 1954).   |
| Unknown dose, 1 case                                     | death 13 hr after suicidal ingestion (Committee on Pesticides, 1951)  |
| Unknown dose, 22 unrelated cases                         | 22 separate cases, including 15 attempted suicides; some complicated by solvents; 3 deaths (Committee on Pesticides, 1951)  |



combining it with another. For example, one would not expect prolonged illness from DDT at a rate of 27 mg/kg. However, when DDT and lindane were ingested in a suicidal attempt at dosages thought to be 27 and 18 mg/kg respectively, clinical remission of convulsions and of liver involvement was delayed until day 20, and the EEG did not return to normal until day 39 (Eskenasy, 1972).

What little is known about the effect of DDT on the human heart fails to show whether cardiac arrhythmia might be a possible cause of death in acute poisoning, as is true in some species of laboratory animals. Palpitations, tachycardia, and "irregular heart action" have been noted in some but not all cases of acute poisoning (Mackerras and West, 1946; Naevested, 1947; Hsieh, 1954).

There have been no accidents or suicides involving respiratory or dermal exposure leading to recognized signs and symptoms of DDT poisoning. This is true even though sufficient respiratory exposure to aerosols or sufficient dermal exposure to solutions can cause poisoning in animals, and the difference is certainly one of dosage.

**Use Experience** The safety record of DDT is phenomenally good [Coulston, 1985; Food and Agriculture Organization/World Health Organization (FAO/WHO), 1985]. It has been used for mass delousing in such a way that the bodies and inner clothing of thousands of people of all ages and states of health were liberally dusted with the compound. By necessity, the applicators worked in a cloud of the material. Other applicators have sprayed the interior of hundreds of millions of homes in tropical and subtropical countries under conditions that Wolfe *et al.* (1959) showed involved extensive dermal and respiratory exposure. A smaller number of people have made or formulated DDT for many years. Extensive experience and numerous medical studies of groups of workers have been reviewed (Hayes, 1959a). Dermatitis was commonly observed among workers who used DDT solutions. The rashes were clearly due to the solvent, especially kerosene. As often happens with rashes caused by petroleum distillates, they were most severe in people when they first started work and cleared in a few days unless contamination was exceptionally severe. A smaller number of workers experienced mild narcotic effects (vertigo and nausea) from solvents when working in confined spaces. Gil and Miron (1949) reported that some persons suffered temporary irritability, fatigue, and other ill-defined symptoms after exposure in the dusty atmosphere of a delousing station, but the relation of these atypical findings to DDT was not clear. With these exceptions due largely to solvents, no illnesses clearly attributable to the formulations, much less to DDT, were revealed by the early studies.

Mild moderate poisoning by DDT itself may have occurred among a group of factory workers exposed to air concentrations of 500–4200 mg/m<sup>3</sup>, but no measurements were made of DDT in blood, fat, or urine. The workers complained of paresthesia of the extremities, headache, dizziness, and some other difficulties less clearly linked to DDT (Aleksieva *et al.*, 1959). Even higher concentrations in air have been associated with

tremor of the tongue and hands as well as with numerous subjective findings (Burkatzkaya *et al.*, 1961).

Ortelee (1958) carried out clinical and laboratory examinations of 40 workers, all of whom were exposed to a number of other pesticides. They had been employed at this work with heavy exposure for 0.4–6.5 years with slightly less exposure for as much as 8 years. Exposure was so intense that during working hours many of the men were coated with a heavy layer of concentrated DDT dust. By comparing their excretion of DDA with that of volunteers given known doses of DDT, it was possible to estimate that the average absorbed dosages of three groups of the workers with different degrees of occupational exposure were 14, 30, and 42 mg/person/day. With the exception of the excretion of DDA and the occurrence of a few cases of minor irritation of the skin and eyes, no correlation was found between any abnormality and exposure to the insecticide. Since very large doses of DDT injure the nervous system and liver of experimental animals, special attention was given to a complete neurological examination and to laboratory tests for liver function. Although a few abnormalities were revealed, none related to DDT was detected.

Laws *et al.* (1967) studied 35 men employed from 11 to 19 years in a plant that had produced DDT continuously and exclusively since 1947 and, at the time of the study, produced 2722 metric tons per month. Findings from medical history, physical examinations, routine clinical laboratory tests, and chest x-ray films did not reveal any ill effects attributable to exposure to DDT. No case of cancer or blood dyscrasia was found among the 35 heavily exposed workers in a DDT factory, nor did the medical records of 63 men who had worked there for more than 5 years reveal these diseases. Two men were employed who had a history of successfully treated cancer before they came to work, but no employee had contracted cancer during the 19 years the plant had operated; during this period, the work force varied from 110 to 135. A study of liver function of the heavily exposed men is discussed near the end of this section.

Measurement of storage offered direct evidence of the men's heavy exposure. The overall range of storage of the sum of isomers and metabolites of DDT in the men's fat was 38–647 ppm, compared to an average of 8 ppm for the general population. Based on their storage of DDT in fat and excretion of DDA in urine, it was estimated that the average daily intake of DDT by the 20 men with high occupational exposure was 17.5–18 mg/person/day, compared to an average of 0.028 mg/person/day then found for the general population. There was significant correlation ( $r = +0.64$ ) between the concentrations of total DDT-related material in the fat and serum of the workers. The concentration in fat averaged 338 times greater than that in serum—a factor about three times greater than that for people without occupational exposure. Compared to people in the general population, workers were found to store a smaller proportion of DDT-related material in the form of DDE; the difference was shown to be related chiefly to intensity rather than duration of exposure. DDE is relatively much less important and DDA much more important as excretory products in



**Table 15.11**  
Average Concentration of DDT and DDE in Fat and Serum and of DDA in the Urine of Workers Engaged in the Manufacture, Formulation, or Use of DDT

| Tissue | Number of workers | DDT (ppm)            | DDE (ppm)            | DDA (ppm) | Total as DDT (ppm) | Estimated exposure (mg/person/day) | Reference                         |
|--------|-------------------|----------------------|----------------------|-----------|--------------------|------------------------------------|-----------------------------------|
| Fat    | 1                 | 648                  | 437                  |           | 1,131              |                                    | Hayes <i>et al.</i> (1956)        |
| Urine  | 10                |                      |                      | 0.57      |                    | 14                                 | Ortelee (1958)                    |
| Urine  | 16                |                      |                      | 1.7       |                    | 30                                 | Ortelee (1958)                    |
| Urine  | 13                |                      |                      | 2.9       |                    | 42                                 | Ortelee (1958)                    |
| Fat    | 3                 | 51                   | 44                   |           | 98                 | 3.6                                | Laws <i>et al.</i> (1967)         |
| Fat    | 12                | 74                   | 50                   |           | 130                | 6.2                                | Laws <i>et al.</i> (1967)         |
| Fat    | 20                | 161                  | 91                   |           | 263                | 18                                 | Laws <i>et al.</i> (1967)         |
| Serum  | 3                 | 0.2113               | 0.1968               |           | 0.5412             | 6.3                                | Laws <i>et al.</i> (1967)         |
| Serum  | 12                | 0.1420               | 0.1454               |           | 0.3548             | 8.4                                | Laws <i>et al.</i> (1967)         |
| Serum  | 20                | 0.3020               | 0.2719               |           | 0.7371             | 17.5                               | Laws <i>et al.</i> (1967)         |
| Urine  | 3                 |                      |                      | 0.41      |                    |                                    | Laws <i>et al.</i> (1967)         |
| Urine  | 12                |                      |                      | 0.6       |                    |                                    | Laws <i>et al.</i> (1967)         |
| Urine  | 20                |                      |                      | 1.27      |                    |                                    | Laws <i>et al.</i> (1967)         |
| Serum  | 18                | 0.573                | 0.506                |           |                    |                                    | Poland <i>et al.</i> (1970)       |
| Serum  | 56                | 0.004 <sup>a,b</sup> | 0.052 <sup>a,b</sup> |           |                    |                                    | Morgan and Roan (1974)            |
| Serum  | 32                | 0.002 <sup>b</sup>   | 0.026 <sup>b</sup>   |           |                    |                                    | Morgan and Roan (1974)            |
| Serum  | 32                | 0.004 <sup>b</sup>   | 0.047 <sup>b</sup>   |           |                    |                                    | Morgan and Roan (1974)            |
| Serum  | 32                | 0.009 <sup>b</sup>   | 0.075 <sup>b</sup>   |           |                    |                                    | Morgan and Roan (1974)            |
| Serum  | 31                | 0.052 <sup>b</sup>   | 0.222 <sup>b</sup>   |           |                    |                                    | Morgan and Roan (1974)            |
| Serum  | 5                 | 0.004 <sup>a</sup>   | 0.021 <sup>a</sup>   |           |                    |                                    | Clifford and Weil (1972)          |
| Serum  | 10                | 0.022                | 0.055                |           |                    |                                    | Clifford and Weil (1972)          |
| Serum  | 4                 | 0.087                | 0.072                |           |                    |                                    | Edmundson <i>et al.</i> (1970)    |
| Blood  | 154               | 0.128                | 0.250                |           |                    |                                    | Edmundson <i>et al.</i> (1969a,b) |
| Urine  |                   |                      |                      | 0.080     |                    |                                    | Edmundson <i>et al.</i> (1975)    |
| Plasma | 23                |                      |                      |           | 0.0389             |                                    | Gracheva (1969)                   |
| Fat    | 18                |                      |                      |           | 5.2–45.2           |                                    |                                   |
| Serum  | 21                | 0.021                | 0.013                |           |                    |                                    | Keil <i>et al.</i> (1972a)        |
| Blood  | 44                |                      |                      |           | 0.761              |                                    | WHO (1973)                        |
| Blood  | 100               |                      |                      |           | 1.273              |                                    | WHO (1973)                        |
| Blood  | 64                | 0.024                | 0.016                |           |                    |                                    | Violante <i>et al.</i> (1986)     |

<sup>a</sup> Control group.

<sup>b</sup> Approximately equal groups arranged by degree of storage.

occupationally exposed men than in men of the general population.

After Laws *et al.* (1967) had completed their study, it was found that the 36 most heavily exposed workers involved had fathered 58 children before they began working at the DDT factory and 93 children afterward (Wilcox, 1967).

By far the largest number of heavily exposed workers whose health has been investigated are those associated with malaria control in Brazil and India (WHO, 1973). In Brazil, periodic clinical examinations were made of 202 sprayers exposed to DDT for 6 or more years, 77 sprayers exposed for 13 years ending in 1959, and 406 controls. In the first examination carried out in 1971, minor differences between exposed and nonexposed groups were observed in some neurological tests, but this result was not confirmed by the second examination in the same year or by subsequent examinations. During a 3-year period, a survey of illnesses requiring medical care during the 6 months preceding each periodic medical examination failed to demonstrate any difference between exposed and control groups. A relatively small number of analyses indicated that the concentration of DDT in the blood of sprayers was about three times higher than that of controls.

In India, the blood levels of 144 sprayers were 7.5–15 times greater than those in controls and were at least as high as those reported for workers who make and formulate DDT elsewhere (see Table 15.11). When the sprayers were examined, no differences from controls were found except that knee reflexes were brisker, slight tremor was more often present, and a timed Romberg test was more poorly performed by the sprayers. The positive results led to the selection of 20 men for reexamination by a neurologist, who concluded that the differences found initially were not real or that the tests had returned to normal within the few months between the two examinations. In any event, the signs were not dosage related, since they showed no correlation with serum levels of DDT. More recently cognitive functions of Indian DDT sprayers have been tested. DDT levels were 8.5 times higher than those in controls and visuomotor functions were significantly depressed (Misra *et al.*, 1984).

Laws *et al.* (1973) made a detailed study of the liver function of 31 men who had made and formulated DDT and who had been the subjects of an earlier study already discussed. Judging from their excretion and storage, the men's exposure was equivalent to an oral intake of DDT at rates ranging from 3.6 to 18 mg/man/day for periods ranging from 16 to 25 years and



averaging 21 years. All tests were in the normal range for total protein, albumin, total bilirubin, thymol turbidity, and retention of sulfobromophthalein sodium (BSP). One man had mild elevation of alkaline phosphatase (16 units) and SGPT (42 units). Another man had an alkaline phosphatase concentration of 14 units, while a third man had an SGPT level of 49 units. The  $\alpha$ -fetoprotein test was negative for all 20 of the men for whom the test was performed.

The induction by DDT of microsomal enzymes of human liver was demonstrated first in workers, and it has been confirmed (see Section 7.4.3 and Therapeutic Use in this section). DDT may be more important than DDE in this regard, as indicated by the fact that Poland *et al.* (1970) observed induction in men with average serum levels of 0.573 and 0.506 ppm for DDT and DDE, respectively, while Morgan and Roan (1974) found no induction in men with corresponding values of 0.052 and 0.222 ppm.

As noted under Therapeutic Use, DDT has been used successfully to induce microsomal enzymes in order to promote metabolism of bilirubin in a case of congenital defect and to promote metabolism of phenobarbital in a case of overdose.

DDT promotes its own metabolism in some species of laboratory animals. That the same is true in humans is indicated by the fact that storage of DDT is relatively less at higher dosages (see Fig. 7.4). However, the metabolism and subsequent excretion of DDT can be promoted even more by phenobarbital and especially diphenylhydantoin (see Metabolism in Section 15.3.1.2) and to a lesser degree by some other drugs (McQueen *et al.*, 1972). Establishment of a reduced equilibrium appeared to require about 2 months. Within this period, the regression of the level of DDT plus DDE on duration of treatment with diphenylhydantoin was highly significant ( $P < 0.001$ ).

In addition to the studies already mentioned regarding workers with extensive storage and/or excretion of DDT as a result of truly heavy exposure to DDT, studies also have been made of a larger number of workers with lesser storage and/or excretion following lesser exposure to DDT but greater exposure to other insecticides. Continuing, meticulous study discussed by Hayes (1975) under Community Studies as well as the work of Tsutsui *et al.* (1974), Ouw and Shandar (1974), and Morgan and Lin (1978) has failed to reveal effects of clinical significance among workers with prolonged, moderate exposure to a wide variety of pesticides. In a review of results for 2620 persons exposed to pesticides and 1049 persons not occupationally exposed, Morgan and Lin (1978) found that, apart from serum pesticide concentrations, the only significant and consistent change associated with occupational exposure was a depression of serum bilirubin. This presumably was a reflection of a slight induction of liver microsomal enzymes. In addition, there was a tendency for serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) to increase with increasing concentrations of DDT plus DDE in the serum, but the differences were small in all instances and statistically significant for SGOT and LDH only.

Wong *et al.* (1984) could find no significant overall cause-specific mortality excess among men potentially exposed at work to DDT from 1935 to 1976. Similarly, a population of 499 persons living downstream from a defunct DDT-manufacturing plant showed no DDT-specific illnesses or ill health despite total DDT serum levels three times the national mean (Kreiss *et al.*, 1981). There was, however, a possible association between serum DDT and serum cholesterol, triglyceride, and  $\gamma$ -glutamyl transpeptidase levels.

A positive linear correlation has been reported for the concentrations of vitamin A and of DDT-related compounds in the serum of men with at least 5 years of occupational exposure to DDT. However, the workers' DDT levels were little higher than those of persons in the general population (see Table 7.15 in Hayes, 1975, and Table 15.11, herein), and their vitamin A levels were within normal limits (Keil *et al.*, 1972b). Perhaps they were better fed than the controls.

Evidence regarding mutagenic activity of DDT and its significance in humans is uncertain. Comparing samples collected in winter and during the peak season of pesticide application, a slight increase in chromatid breaks was reported in the cultured lymphocytes of workers exposed to a wide variety of insecticides said to include DDT. A somewhat larger increase was reported for men exposed mainly to herbicides (Yoder *et al.*, 1973). The paper failed to explain why exposure to DDT was claimed at a time when its use was banned. In another study, lymphocytes cultured from workers with an average DDT plasma level of 0.999 ppm showed significantly more chromosomal and chromatid aberrations than did cells cultured from controls with an average plasma level of 0.275 ppm. The difference was not significant in other comparisons in which the average plasma levels were 1.030 versus 0.380 ppm and 0.240 versus 0.030 ppm, respectively (Rabello *et al.*, 1975). Examination of all of the data presented by the authors suggests that a simple dosage-effect relationship was present, with a detectable effect starting somewhere between 0.2 and 0.4 ppm and increasing at levels higher than 0.4 ppm. Some chromosomal aberrations have also been observed with human lymphocyte cultures by Preston *et al.* (1981), but DDT did not cause unscheduled DNA synthesis in SV40-transformed human cells (Ahmed *et al.*, 1977).

Although there is a lot of evidence against DDT's causing liver cancer in humans in Western countries, there is still the outside possibility of it acting as a promoter of potent carcinogens. Aflatoxin is a well-known human carcinogen in areas of Southeast Asia such as Thailand, where DDT and other chlorinated insecticides are still widely used. In Denmark, Unger and Olsen (1980) have found significantly higher levels of DDE in adipose tissue from terminal cancer patients than in tissue from patients who died from other causes. In the United States, DDT and DDE levels were measured in 919 subjects in 1974 and 1975. After 10 years there was no correlation between these levels and overall mortality or cancer mortality except a slight correlation with respiratory cancer death (Austin *et al.*, 1989). Of course, increased storage often correlates with emaciation of whatever cause (Hayes, 1975).



**Atypical Cases of Various Origins** It has been alleged that DDT causes or contributes to a wide variety of diseases of humans and animals not previously recognized as associated with any chemical. Such diseases included cardiovascular disease, cancer, atypical pneumonia, retrolental fibroplasia, poliomyelitis, hepatitis, and "neuropsychiatric manifestations" (Biskind, 1952, 1953; Biskind and Bieber, 1949). Without exception, the causes of these diseases were unknown or at least unproved at the time of the allegation. Needless to say, the charge that DDT predisposed to poliomyelitis was dropped after the disease was controlled through the use of vaccines. Unfortunately, there is no immediate possibility of controlling cardiovascular disease, cancer, or many of the less common conditions in humans that have been ascribed to DDT. In the meantime, such irresponsible claims could produce great harm and, if taken seriously, even interfere with scientific search for true causes and realistic means of preventing the conditions in question.

"Highly sensitive subjects" were said to experience visual disturbances, headache, perceptual abnormalities, muscular weakness, and decrease in mental and physical activity when a food oil solution containing as little as 10 ppm DDT was held beneath their nostrils. Ordinary people could not distinguish the odor of solutions containing up to 10,000 ppm from that of plain oil, and they were unaffected (Kailin and Hastings, 1966). This finding is unconfirmed; if such highly sensitive subjects exist, they are excessively rare.

There is a strong tendency to blame blood dyscrasias, other manifestations of "hypersensitivity," and, in fact, many diseases of unknown cause on any new chemical that gains widespread attention. DDT was no exception. A review of the early literature (Hayes, 1959a) indicates that blood dyscrasias and an unbelievable range of other diseases were, in fact, blamed on DDT. Only a circumstantial relationship ever was established between these diseases and exposure to DDT, and this remains true of the small number of reports of blood dyscrasias (Schüttmann, 1968; Murray *et al.*, 1973) or angioneurotic edema (Vanat and Vanat, 1971) that appeared later. As the novelty wore off, fewer new reports appeared linking DDT to diseases of unknown cause, although the use of DDT increased greatly. It is true that available tests do not make it possible to exclude a particular compound as a cause of an isolated case of blood dyscrasia (see Section 8.1.4.1). However, it is noteworthy that the rate at which these disorders occur has remained essentially unchanged since before DDT was introduced (see Fig. 7.10 in Hayes, 1975).

Eight cases of chronic liver disease have been reported among men with prolonged occupational exposure to DDT and BHC in connection with either their manufacture or use (Schüttmann, 1968). The cases were well studied individually but not epidemiologically.

There are a few reports of acute illness among workers attributed to exposure to mixtures of DDT and other materials. Insofar as the dosage was very large, as in certain accidents that have occurred involving individuals or groups in the general population, one would expect similar results. However, in at

least one instance, headache, dizziness, nausea, vomiting, pain and numbness of the limbs, and general weakness beginning 1–1.5 hr after entering a treated field (Kolyada and Mikhail'chenkova, 1973) was suggestive of food poisoning or hysteria.

Finally, there are studies of workers exposed to DDT and various other pesticides that are reported to have produced a variety of subjective and even objective medical findings. Interpretation of these reports is difficult because (a) the findings do not resemble those of poisoned animals or of persons poisoned as a result of accident or suicide and (b) the papers fail to report how the medical findings and the absenteeism of the pesticide workers compared with those of workers of comparable age, sex, and exertion who were not exposed to chemicals. The fact that the workers in question were exposed to mixtures of pesticides is not in itself an explanation because many workers, on whom careful study revealed no consistent difference from the controls, were exposed to mixtures.

The reports under discussion tend to fall into two sets, those involving general debility and those involving a single organ or system. Conditions representative of general debility include dermatitis, subtle blood changes, general weakness, palpitations, functional angiospasm, headache, dizziness, diminished appetite, vomiting, lower abdominal pain, chronic gastritis, benign chronic hepatitis, insomnia, a sympathetic vascular/asthenic syndrome, vegetative dystonia, and confusion (Jovčić and Ivanuš, 1968; Model', 1968; Kostjuk and Mukhtarova, 1970; Bezuglyi *et al.*, 1973).

Organs, systems, or functions that have been studied apparently by specialists and to the complete exclusion of other organs, systems, or functions of the same workers include the respiratory system (Boiko and Krasnyuk, 1969), liver (Krasnyuk *et al.*, 1967; Bezuglyi and Kaskevich, 1969), stomach (Krasnyuk and Platonova, 1969; Platonova, 1970), kidneys (Krasnyuk *et al.*, 1968), labor and puerparium (Komarova, 1970; Nikitina, 1974), adrenals (Baksheyev, 1973), and skin (Karimov, 1969, 1970). An indication that the difficulties under discussion are not serious is their reversal or prophylaxis by means of diet. Leshchenko and Polonskaia (1969) described in detail two dietary supplements composed of ordinary foods plus sea kale and a selection of vitamins and trace metals. Organochlorine workers who received these diet products showed a normalization of protein metabolism manifested by an increase in total serum protein, improved lipid metabolism, and enriched vitamin and trace element supply in the organism. All of these effects led to an improvement of the detoxifying function of the liver, which was viewed as the most frequent site of adverse effects of exposure to organochlorine compounds. The frequency and degree of olfactory disorders, especially ability to detect peppermint and acetic acid in an olfactory analyzer, were reported to be greater among persons exposed to pesticides and increased with duration of exposure (Salikhodzhaev and Fershtat, 1972). Whether any of the persons exposed to pesticides experienced any clinical difficulty or social inconvenience associated with olfactory sensation is not clear.



**Dosage Response** The clinical effects of different dosage levels of DDT in humans are summarized in Tables 7.24 in Hayes (1975) and in Tables 15.8 and 15.10, herein. The degree of storage determined by different dosage levels of DDT has been summarized in Fig. 7.4, and details regarding higher than normal dosage rates are given in Table 15.9. A clinically useful degree of induction of microsomal enzymes was obtained with a DDT dosage of 1.5 mg/kg/day for 6 months (see paragraph on Therapeutic Use). As discussed under Use Experience and in Section 7.4.3, workers who absorbed a dosage of about 0.25 mg/kg/day showed demonstrable but only slight induction. Workers with less exposure as indicated by lower serum levels of DDT showed no detectable induction.

**Storage in Fat** The highest reported storage of DDT and related compounds remains that of a healthy worker whose fat contained DDT and DDE (as DDT) at concentrations of 648 and 483 ppm, respectively (Hayes *et al.*, 1956). Laws *et al.* (1967) reported considerably lower storage values among the most exposed persons in a DDT manufacturing plant (see Table 15.11). An important point evident from the table is that, whereas almost all investigations of workers are said to have been carried out on "heavily exposed" populations (or words to that effect), some of the groups studied had absorbed little more DDT than is absorbed by the general population—especially the general population of some tropical countries—as recorded in Table 15.12.

The first evidence that human beings metabolize a part of the DDT they absorb to DDE was obtained from the analysis of fat from a worker (Mattson *et al.*, 1953). The accumulation of DDE relative to total DDT-related compounds is best illustrated in humans. Of the total DDT stored in the fat of workers exposed to technical DDT (about 4% DDE) for 11–19 years, only 38% was in the form of DDE, and, of course, some of that DDE came from their diets including meat (Laws *et al.*, 1967). In India, where many people avoid meat but may consume milk, cheese, and eggs, 34–41% of total DDT stored by people without special exposure was DDE (Dale *et al.*, 1965). In the United States, during a time when DDT residues in food were decreasing, the proportion of total DDT in the form of DDE increased from about 60% in 1955 to about 80% in 1970; during the same interval the concentration of total DDT in body fat decreased from about 15 ppm to less than 10 ppm as recorded in Table 7.10 in Hayes (1975). By 1980, DDE constituted 86.7% of total DDT in one population (Kreiss *et al.*, 1981). Thus, a low proportion of DDE indicates a relatively high intake of parent DDT and relatively few years for metabolism of stored DDT to DDE.

A number of factors, especially dosage, age, sex, race, and various disease states, have been discussed in connection with the storage and excretion of DDT by people (see Section 7.2.3), but only dosage has been shown to be of practical importance.

DDT and related compounds are stored at much lower rates in the general population than in persons with occupational exposure. However, these relatively low levels of storage constitute one of the most important aspects of the measurable

effects of pesticides on people. Consequently, these values have been presented and discussed in detail (see Section 7.2.2.2 and Table 15.12). Briefly, storage of total DDT in the body fat of ordinary people in the United States increased from 5.3 ppm in 1950 to about 15.6 ppm in 1955 and 1956. Thereafter, the levels decreased gradually, albeit somewhat irregularly, to about 8 ppm in 1970 and to 3 ppm in 1980 (see Fig. 7.3). In annual surveys in the United States based on 898–1920 samples per year, the geometric mean levels for total DDT in adipose tissue on a lipid basis were 7.88, 7.95, 6.88, 5.89, and 5.02 ppm for fiscal years 1970, 1971, 1972, 1973, and 1974, respectively. For each year, the values were higher for older age groups and higher for black than for white people. During fiscal year 1974, the values for persons 0–14, 15–44, and 45 years old or more were 2.15, 4.91, and 6.55 ppm, respectively, for white people and 4.02, 9.18, and 11.91 ppm, respectively, for black people (Kutz *et al.*, 1977). The values would have been somewhat lower if they had been based on wet weight.

It has been calculated that if exposure to DDT ceased it would take 10–20 years for DDT to disappear from a person but that DDE would persist throughout the life span (Morgan and Roan, 1977).

**Storage in Blood** No information is available on blood levels of DDT in persons poisoned by the compound. Concentrations measured in the blood or serum of workers are shown in Table 15.11. The highest value for total DDT in serum reported from several countries was 2.2017 ppm (with an average of 0.7371 ppm) based on gas chromatography (Laws *et al.*, 1967). A different situation is indicated by a report by Genina *et al.* (1969), who used a total chloride method to analyze samples of blood from controls and from persons with occupational exposure to DDT, polychloroprene, and BHC. These authors reported chlororganic compounds as high as 38.4 ppm in the blood of warehousemen. This concentration is about 20 times the highest value found by the same authors in their control group. The factor of 20 is not remarkable, but (especially in view of the fact that polychloroprene and BHC are excreted more readily than DDT and DDE) values as high as 9 ppm in the controls are completely unexpected. Whether the difference was based on massive exposure or analytical factors is unclear.

The concentrations of DDT in the blood of ordinary people are shown in Table 15.13 and are discussed in Section 7.2.2.3. It is of interest that although each person without special exposure to DDT has relatively constant serum levels of DDT and DDE, and DDE values differ more than the DDT values from person to person (Apple *et al.*, 1970). Whether this reflects differences in metabolism or differences in past exposure is unclear. Kreiss *et al.* (1981) have shown that DDE in serum samples of a community exceptionally exposed to DDT increased with age of the individual.

Surveys have demonstrated a gradual decline in the concentrations of DDT and related compounds in human fat. Presumably a similar decline has occurred in the levels of these compounds in human serum, but apparently no surveys have been carried out and, therefore, no direct evidence is available.

When storage of DDT has been found to be greater in black



Table 15.12

Concentrations of Some Chlorinated Hydrocarbon Pesticides in Body Fat of the General Population of Different Countries

| Country                    | Year      | Number of samples | Total DDT (ppm)      | Total BHC (ppm)     | Dieldrin (ppm)      | Heptachlor epoxide (ppm) | References                              |
|----------------------------|-----------|-------------------|----------------------|---------------------|---------------------|--------------------------|---|
| North America<br>Canada    | 1959-1960 | 62                | 4.9                  |                     |                     |                          | Read and McKinley (1961)                |
|                            | 1966      | 47                | 4.39                 |                     |                     |                          | Brown (1967)                            |
|                            | 1966      | 35                |                      |                     | 0.22                |                          | Brown (1967)                            |
|                            | 1966      | 42                |                      | 0.07                |                     |                          | Brown (1967)                            |
|                            | 1966      | 22                |                      |                     |                     | 0.14                     | Brown (1967)                            |
|                            | 1967-1968 | 51                | 5.86                 |                     |                     |                          | Kadis <i>et al.</i> (1970)              |
|                            | 1969      | 221               | 4.85                 | 0.015               | 0.122               | 0.040                    | Ritchey <i>et al.</i> (1973)            |
|                            | unknown   |                   |                      |                     | ≤1.810              | ≤0.518                   | Larsen <i>et al.</i> (1971)             |
|                            | unknown   |                   |                      |                     | ≤0.087              | ≤0.136                   | Larsen <i>et al.</i> (1971)             |
|                            | unknown   |                   | 5.83                 |                     |                     |                          | Brown and Chow (1975)                   |
|                            | 1972      | 168               | 2.57                 | 0.65                | 0.069               | 0.043                    | Mes <i>et al.</i> (1977)                |
|                            | 1976      | 99                | 2.06                 | 0.158               | 0.049               | 0.037                    | Mes <i>et al.</i> (1982)                |
|                            | 1979-1981 | 91                | 3.78                 |                     | 0.036               | 0.035                    | Williams <i>et al.</i> (1984)           |
|                            | 1974      | 33                | 3.3                  |                     | 0.09                | 0.12                     | Jensen and Clausen (1979)               |
| Greenland<br>United States | <1942     | 10                | ND <sup>a</sup>      |                     |                     |                          | Hayes <i>et al.</i> (1958)              |
|                            | 1950      | 75                | 5.3                  |                     |                     |                          | Laug <i>et al.</i> (1951)               |
|                            | 1955      | 49                | 19.9                 |                     |                     |                          | Hayes <i>et al.</i> (1956)              |
|                            | 1954-1956 | 61                | 11.7                 |                     |                     |                          | Hayes <i>et al.</i> (1958)              |
|                            | 1956      | 36                | 15.6                 |                     |                     |                          | Hayes <i>et al.</i> (1971)              |
|                            | 1961-1962 | 130               | 12.7                 |                     |                     |                          | Quinby <i>et al.</i> (1965a)            |
|                            | 1961-1962 | 28                | 6.7                  | 0.20                | 0.15                |                          | Dale and Quinby (1963)                  |
|                            | 1962-1963 | 282               | 11.1                 | 0.57                | 0.11                |                          | Hoffman <i>et al.</i> (1964)            |
|                            | 1964      | 64                | 7.6                  |                     | 0.31                | 0.10                     | Zavon <i>et al.</i> (1965)              |
|                            | 1964      | 25                | 10.3                 | 0.60                | 0.29                | 0.24                     | Hayes <i>et al.</i> (1965)              |
|                            | 1964-1965 | 18                | 9.0                  |                     | 0.002-0.8           |                          | Schafer and Campbell (1966)             |
|                            | 1964-1965 | 42                | 10.6                 |                     |                     |                          | Radomski <i>et al.</i> (1968)           |
|                            | 1964-1965 | 42                |                      |                     | 0.215               |                          | Fiserova-Bergerova <i>et al.</i> (1967) |
|                            | (Florida) |                   |                      |                     |                     |                          | Hoffman <i>et al.</i> (1967)            |
|                            | (Chicago) | 1962-1966         | 221-994 <sup>b</sup> | 0.48                | 0.14                | 0.16                     | Davies <i>et al.</i> (1968)             |
|                            |           | 1964-1965         | 12                   |                     |                     |                          | Davies <i>et al.</i> (1968)             |
|                            |           | 1965-1967         | 17                   |                     |                     |                          | Davies <i>et al.</i> (1968)             |
|                            |           | 1965-1967         | 90                   |                     |                     |                          | Davies <i>et al.</i> (1968)             |
|                            |           | 1965-1967         | 17                   |                     |                     |                          | Casarett <i>et al.</i> (1968)           |
|                            | (Hawaii)  | 1965-1967         | 30                   |                     | 0.0300              | 0.0220                   | Casarett <i>et al.</i> (1968)           |
|                            | (Hawaii)  | 1965-1967         | 29                   |                     | 0.630               | 0.0320                   | Casarett <i>et al.</i> (1968)           |
|                            | (Hawaii)  | 1965-1967         | 30                   |                     | 0.0270              | 0.0270                   | Casarett <i>et al.</i> (1968)           |
|                            |           | 1965-1967         | 146                  |                     | 0.22                |                          | Edmundson <i>et al.</i> (1968)          |
|                            |           | 1965-1967         | 42                   |                     | 0.21                |                          | Radomski <i>et al.</i> (1968)           |
|                            |           | 1965-1967         | 733                  | 0.29                | 0.15                | 0.05                     | A. Yobs, personal communication (1969)  |
| (11 states)                | 1965-1967 |                   | 6.22                 |                     |                     |                          | A. Yobs, personal communication (1969)  |
| (20 states)                | 1965-1967 | 3104              | 7.67                 | 0.24                | 0.10                | 0.05                     | Morgan and Roan (1970)                  |
| (Arizona)                  | 1966-1968 | 70                | 6.69                 |                     | 0.14                |                          | Warnick and Carter (1972)               |
|                            | 1967-1971 | 103               | 7.1                  |                     |                     |                          | Wyllie <i>et al.</i> (1972)             |
| (Idaho)                    | 1970      | 200               | 9.9                  | 0.3                 | 0.2                 | 0.1                      | Kutz <i>et al.</i> (1974b)              |
|                            | 1970      | 1412              | 7.87 <sup>c,d</sup>  | 0.43 <sup>c,d</sup> | 0.18 <sup>c,d</sup> | 0.09 <sup>c,d</sup>      | Burns (1974)                            |
| (Texas)                    | 1969-1972 | 221               | 23.18                | 1.29                | 0.35                |                          | Kutz <i>et al.</i> (1977)               |
|                            | 1970      | 1410              | 7.88 <sup>d</sup>    |                     |                     |                          | Kutz <i>et al.</i> (1977)               |
|                            | 1971      | 1612              | 7.95 <sup>d</sup>    |                     |                     |                          | Kutz <i>et al.</i> (1977)               |
|                            | 1972      | 1919              | 6.88 <sup>d</sup>    |                     |                     |                          | Kutz <i>et al.</i> (1977)               |
|                            | 1973      | 1092              | 5.89 <sup>d</sup>    |                     |                     | 0.30 <sup>d</sup>        | Domanski <i>et al.</i> (1977)           |
| (Pennsylvania, black)      | 1973-1974 | 14                | 14.0 <sup>d</sup>    |                     |                     |                          |   |
|                            |           |                   |                      |                     | 0.24 <sup>d</sup>   |                          | Domanski <i>et al.</i> (1977)           |
| (Pennsylvania, white)      | 1973-1974 | 13                | 5.1 <sup>d</sup>     |                     |                     |                          |   |
|                            |           |                   |                      |                     |                     |                          | Kutz <i>et al.</i> (1977)               |
|                            | 1974      | 898               | 5.02 <sup>d</sup>    |                     | 0.17                | 0.16                     | Greer <i>et al.</i> (1980)              |
| (Louisiana)                | 1977      | 22                | 8.29                 |                     | 0.15                | 0.06                     | Barquet <i>et al.</i> (1981)            |
| (Florida)                  | unknown   | 10                | 6.71                 |                     |                     |                          |   |

(continued)



Table 15.12 (Continued)

| Country                    | Year      | Number of samples | Total DDT (ppm)    | Total BHC (ppm)   | Dieldrin (ppm)    | Heptachlor epoxide (ppm) | References                                |
|----------------------------|-----------|-------------------|--------------------|-------------------|-------------------|--------------------------|---|
| Central America and Mexico |           |                   |                    |                   |                   |                          |   |
| Costa Rica                 | 1984?     | 30                | 59.2 <sup>d</sup>  |                   | 0.16 <sup>d</sup> | 0.38 <sup>d</sup>        | Barquero and Constenla (1986)             |
| Mexico                     | 1975      | 19                | 21.47 <sup>d</sup> |                   | 0.06 <sup>d</sup> |                          | Albert <i>et al.</i> (1980)               |
| South America              |           |                   |                    |                   |                   |                          |   |
| Argentina                  | 1967      | 37                | 13.2               | 2.44              | 0.38              | 0.192                    | Wassermann <i>et al.</i> (1968a)          |
| Venezuela                  | 1964      | 38                | 10.3               | 0.16              | 0.60              |                          | W. E. Dale, personal communication (1971) |
| Brazil                     | 1969–1970 | 38                | 4.1                |                   |                   |                          | Wassermann <i>et al.</i> (1972c)          |
| Europe                     |           |                   |                    |                   |                   |                          |   |
| Austria                    | 1966      |                   | 6.33               | 1.9               | 0.1               |                          | Pesendorfer <i>et al.</i> (1973)          |
| Belgium                    | 1964      | 20                | 3.3                |                   |                   |                          | Maes and Heyndrickx (1966)                |
|                            | 1975      | 60                | 8.29               | 0.76              | 0.26              | 0.38                     | Djonckheere <i>et al.</i> (1977)          |
| Czechoslovakia             | 1963–1964 | 229               | 9.6                |                   |                   |                          | Halacka <i>et al.</i> (1965)              |
|                            | 1975–1976 | 13                | 2.26–3.97          | 2.55–20.95        |                   |                          | Dubsky <i>et al.</i> (1977)               |
| Denmark                    | 1965      | 18                | 3.3                |                   | 0.20              |                          | Weihe (1966)                              |
|                            | 1974      | 17                | 1.8                |                   | 0.09              | 0.08                     | Jensen and Clausen (1979)                 |
| England                    | 1961–1962 | 131               | 2.2                |                   | 0.21              |                          | Hunter <i>et al.</i> (1963)               |
|                            | 1963–1964 | 66                | 3.3                | 0.42              | 0.26              | 0.1                      | Egan <i>et al.</i> (1965)                 |
|                            | 1964      | 100               | 3.9                | 0.02              | 0.21              | 0.1                      | Robinson <i>et al.</i> (1965)             |
|                            | 1964      | 44                | 4.0                |                   | 0.22              |                          | Robinson and Hunter (1966)                |
|                            | 1965      | 101               | 2.85               | 0.19              | 0.34              |                          | Cassidy <i>et al.</i> (1967)              |
|                            | 1965–1967 | 248               | 3.00               | 0.31              | 0.21              | 0.04                     | Abbott <i>et al.</i> (1968)               |
| United Kingdom             | 1969–1971 | 201               | 2.5                | 0.29              | 0.16              | 0.03                     | Abbott <i>et al.</i> (1972)               |
|                            | 1976–1977 | 236               | 2.6                | 0.33              | 0.11              | 0.03                     | Abbott <i>et al.</i> (1981)               |
|                            | 1982–1983 | 187               | 1.54               | 0.30              | 0.08              |                          | Abbott <i>et al.</i> (1985)               |
| Finland                    | 1972–1974 | 73                | 2.5                |                   |                   |                          | Hattula <i>et al.</i> (1976)              |
|                            | 1983      | 65                | 0.33               |                   |                   | 0.002                    | Mussalo-Rauhama <i>et al.</i> (1984)      |
| France                     | 1961      | 10                | 5.2                | 1.19              |                   |                          | Hayes <i>et al.</i> (1963)                |
| Germany (East)             | 1966–1967 | 100               | 13.1               | 0.16              |                   |                          | Engst <i>et al.</i> (1967)                |
|                            | 1958–1959 | 60                | 2.3                |                   |                   |                          | Maier-Bode (1960)                         |
| Germany (West)             | 1970      | 20                | 3.6                | 0.45              |                   |                          | Acker and Schulte (1970)                  |
|                            |           |                   | 3.8                | 0.5               | 0.2               |                          | Acker and Schulte (1971)                  |
|                            |           | 10                | 4.24               | 2.9               | 0.11              | 0.097                    | Acker and Schulte (1974)                  |
|                            |           | 10                | 4.77               | 8.2               | 0.17              | .12                      | Acker and Schulte (1974)                  |
|                            |           | 10                | 5.42               | 5.9               | 0.091             | 0.062                    | Acker and Schulte (1974)                  |
|                            |           | 10                | 8.36               | 4.8               | 0.082             | 0.085                    | Acker and Schulte (1974)                  |
|                            |           | 10                | 7.80               | 6.4               | 0.23              | 0.096                    | Acker and Schulte (1974)                  |
| (workers)                  | 1979?     | 8                 |                    | 54.5 <sup>d</sup> |                   |                          | Baumann <i>et al.</i> (1980)              |
| Hungary                    | 1960      | 48                | 12.4               |                   |                   |                          | Denes (1962)                              |
|                            | 1964      | 15                |                    |                   | 0.16              |                          | Denes (1966)                              |
|                            | 1969      |                   | 13.7               | 2.30              |                   |                          | Berend <i>et al.</i> (1970)               |
|                            | 1970      |                   | 18.9               | 0.76              |                   |                          | Soos <i>et al.</i> (1972)                 |
| Italy                      | 1965      | 9                 | 5.0                |                   | 0.594             |                          | Kanitz and Castello (1966)                |
|                            | 1965–1966 | 18                | 10.86              | 2.25              | 0.84              | 0.46                     | Paccagnella <i>et al.</i> (1967)          |
|                            | 1966      | 22                | 15.48              | 0.08              | 0.68              | 0.23                     | Del Vecchio and Leoni (1967)              |
|                            | 1970?     | 31                | 16.75              | 0.02              | 0.10              |                          | Prati and Del Dot (1971)                  |
|                            | 1983–1984 | 26                | 8.99 <sup>e</sup>  |                   |                   |                          | Focardi <i>et al.</i> (1986)              |
| Netherlands                | 1964      | 20                | 7.7                |                   |                   |                          | Wit (1964)                                |
|                            | 1966      | 11                | 2.22               | 0.11              | 0.20              | 0.01                     | De Vlieger <i>et al.</i> (1968)           |
| Norway                     |           | 56                | 3.2                |                   |                   |                          | Bjerk (1972)                              |
|                            | 1972      | 7                 | 10                 |                   |                   |                          | Kveseth <i>et al.</i> (1979)              |
|                            | 1975–1976 | 58                | 0.75–2.60          |                   |                   |                          | Brevik and Bjerk (1978)                   |
|                            | 1981–1982 | 16                | 0.448              |                   |                   |                          | Skaare <i>et al.</i> (1988)               |

(continued)



Table 15.12 (Continued)

| Country              | Year      | Number of samples | Total DDT (ppm)   | Total BHC (ppm)    | Dieldrin (ppm) | Heptachlor epoxide (ppm) | References                                  |
|----------------------|-----------|-------------------|-------------------|--------------------|----------------|--------------------------|---|
| Poland               | 1965      | 72                | 13.4              |                    |                |                          | Bronisz <i>et al.</i> (1967)                |
|                      | 1970      | 70                | 11.4              | 0.5                | ND             |                          | Juskiewicz and Stec (1971)                  |
|                      | 1972      | 15                | 5.23              |                    |                |                          | Bojanowska <i>et al.</i> (1973)             |
|                      | 1977-1978 | 100               | 4.47              | 0.216              |                |                          | Syrowatka <i>et al.</i> (1979)              |
| Romania              |           | 20                |                   | 0.48-42            |                |                          | Mandroi and Iordachescu (1971)              |
|                      | 1972-973  |                   | 2.41              |                    |                |                          | Ciube (1976)                                |
| Spain                | 1966      | 41                | 15.7              |                    |                |                          | Llinares and Wasserman (1968)               |
|                      | 1970s     | 40                | 4.549             | 0.062              | 0.15           | 0.015                    | Herrea-Martache <i>et al.</i> (1978)        |
|                      | 1980s     | 55                | 8.95              | 1.38               | 0.27           | 0.16                     | To-Figueras <i>et al.</i> (1986)            |
| Switzerland          |           | 12                | 1.9-16.3          | 0.3-1.8            | 0.07-0.57      |                          | Zimmerli and Marek (1973)                   |
| USSR                 |           | 41                | 8.06              |                    |                |                          | Vas'Kovaskaja and Komarova (1963)           |
|                      |           | 197               | 8.8658-15.4794    | 2.15               |                |                          | Vas'Kovskaja (1969)                         |
| Africa               |           |                   |                   |                    |                |                          |   |
| Nigeria              | 1967      | 43                | 8.8               |                    |                |                          | Wassermann <i>et al.</i> (1968b)            |
|                      | 1969      | 41                | 6.5               | 0.19               |                |                          | Wassermann <i>et al.</i> (1972c)            |
| Kenya                |           | 83                | 5.4               |                    | 0.1            | 0.1                      | Wassermann <i>et al.</i> (1972b)            |
| South Africa (Bantu) | 1969      | 73                | 5.94              | 1.93               | 0.034          | 0.01                     | M. Wassermann <i>et al.</i> (1970b)         |
| (white)              | 1969      | 41                | 7.16              | 3.27               | 0.047          | 0.01                     | M. Wassermann <i>et al.</i> (1970b)         |
| Uganda               |           | 75                | 2.9               | 0.1                |                | 0.02                     | Wassermann <i>et al.</i> (1974a)            |
| Asia                 |           |                   |                   |                    |                |                          |   |
| Burma                | unknown   | 43                | 0.3-7.0           |                    |                |                          | Shure and Law (1977)                        |
| India                | 1964      | 35-67             | 26                | 1.43               | 0.04           |                          | Dale <i>et al.</i> (1965)                   |
|                      | 1964      | 16                | 13                |                    |                |                          | Dale <i>et al.</i> (1965)                   |
|                      | unknown   | 94                | 21.8              |                    |                |                          | Ramachandran <i>et al.</i> (1973)           |
|                      | 1975-1976 | 100               | 0.45              |                    |                |                          | Mukherjee <i>et al.</i> (1980)              |
|                      | 1981?     | 6                 | 1.754             | 2.344              |                |                          | Kaphalia and Seth (1983)                    |
|                      | 1976      | 14                | 4.7               |                    |                |                          | Bhaskaran <i>et al.</i> (1979)              |
| Iran                 | 1974-1976 | 170               | 8.13              | 0.26               | 0.049          |                          | Hashemy-Tonkabony and Soleimani-Amin (1978) |
|                      |           |                   |                   |                    |                |                          | Wassermann <i>et al.</i> (1965)             |
| Israel               | 1963-1964 | 254               | 19.2              |                    |                |                          | Wassermann <i>et al.</i> (1967)             |
|                      | 1965-1966 | 71                | 4.6               |                    |                |                          | Wassermann <i>et al.</i> (1967)             |
|                      | 1965-1966 | 133               | 8.2               |                    |                |                          | Wassermann <i>et al.</i> (1974b)            |
|                      | 1967-1971 | 63                | 14.4              |                    |                |                          | Curley <i>et al.</i> (1970)                 |
| Japan                | 1968-1969 | 241               | 2.4               | 0.12-1.28          | 0.13           | 0.02                     | Nishimoto <i>et al.</i> (1970)              |
|                      | 1969-1970 | 74                | 6.92              | 12.17              | 0.46           | 0.01                     | Doguchi <i>et al.</i> (1971)                |
|                      | 1970      | 21                | 3.69              |                    | 0.33           |                          | Suzuki <i>et al.</i> (1973)                 |
|                      | 1970      |                   | 4.499             | 2.420              | 0.163          |                          | Suzuki <i>et al.</i> (1973)                 |
|                      | 1971      |                   | 2.694             | 3.001              | 0.208          |                          | Kasai <i>et al.</i> (1972)                  |
|                      | 1971      | 30                | 12.859            | 6.160              | 0.098          |                          | Suzuki <i>et al.</i> (1973)                 |
|                      | 1972      |                   | 4.001             | 3.698              | 0.429          |                          | Kasai <i>et al.</i> (1972)                  |
|                      | 1972      | 42                | 5.992             |                    | 0.310          |                          | Kawanishi <i>et al.</i> (1973)              |
|                      | 1973      | 60                | 6.44              | 2.659              | 0.129          |                          | Inoue <i>et al.</i> (1974)                  |
|                      | 1974      | 17                | 6.87              | 3.0                |                |                          | Fukano and Doguchi (1977)                   |
|                      | 1974      | 30                | 3.59              | 2.36               |                |                          |   |
|                      |           |                   |                   | 11.90 <sup>d</sup> |                |                          | Mori <i>et al.</i> (1983)                   |
|                      | 1974      | 20                | 9.25 <sup>d</sup> | 4.92 <sup>d</sup>  |                |                          | Mori <i>et al.</i> (1983)                   |
|                      | 1976      | 22                | 4.79 <sup>d</sup> | 3.77 <sup>d</sup>  |                |                          | Mori <i>et al.</i> (1983)                   |
|                      | 1981      | 46                | 4.04 <sup>d</sup> | 0.48               | 0.47           |                          | Mughal and Rahman (1973)                    |
| Pakistan             |           | 60                | 25.0              |                    |                |                          |   |

(continued)



Table 15.12 (Continued)

| Country     | Year      | Number of samples | Total DDT (ppm)   | Total BHC (ppm)   | Dieldrin (ppm) | Heptachlor epoxide (ppm) | References                       |
|-------------|-----------|-------------------|-------------------|-------------------|----------------|--------------------------|----------------------------------|
| Thailand    | 1969–1970 | 77                | 12.6              | 0.2               | 0.2            |                          | Wassermann <i>et al.</i> (1972c) |
| Turkey      | 1984–1985 | 48                | 7.12 <sup>d</sup> | 1.72 <sup>d</sup> |                |                          | Karakaya <i>et al.</i> (1987)    |
| Oceania     |           |                   |                   |                   |                |                          |                                  |
| Australia   | 1965      | 53                | 1.81              |                   | 0.05           |                          | Bick (1967)                      |
|             | 1965–1966 | 46                | 10.2              |                   |                |                          | Wassermann <i>et al.</i> (1968a) |
|             | 1965–1966 | 12                | 10.5              | 0.68              | 0.67           | 0.02                     | Wassermann <i>et al.</i> (1968a) |
|             | 1971      | 75                | 4.94              |                   | 0.21           |                          | Brady and Siyali (1972)          |
|             | 1985–1986 | 292               | 3.72              |                   | 0.13           |                          | Ahmad <i>et al.</i> (1988)       |
| New Zealand | 1963–1964 | 45                |                   | 0.49              |                |                          | Dacre (1969)                     |
|             | 1966      | 52                | 5.8               |                   | 0.27           |                          | Brewton and McGrath (1967)       |
|             | 1965–1969 | 254               | 14.6              |                   | 0.35           |                          | Copplestone <i>et al.</i> (1973) |

<sup>a</sup> Not detected.<sup>b</sup> Different numbers of samples examined for different compounds.<sup>c</sup> Geometric mean.<sup>d</sup> Lipid basis.<sup>e</sup> Dry weight basis.

people, the difference could be accounted for by greater exposure (Hayes, 1975; D'Ercole *et al.*, 1976). However, Sandifer (1974), who found that the concentrations of DDT in the sera of blacks was two to three times greater than those in whites, also found a significant correlation between total DDT and deficiency of glucose-6-phosphate dehydrogenase, a condition much more common in blacks than whites. Thus, a genetic factor in the storage of DDT appears possible, but additional evidence would be necessary to confirm it.

Whether the high storage in blacks is strictly environmental or partly genetic, it is certain that as high or higher levels have been recorded among several groups of rural blacks in different parts of the southeastern United States than were reported by Kreiss *et al.* (1981) among blacks in Triana, Alabama, who had mean values of 0.096 and 0.062 ppm for total DDT in the serum of males and females, respectively. Other average values for rural blacks have included 0.101 ppm for women (D'Ercole *et al.*, 1976), 0.072 and 0.066 ppm for children and mothers, respectively (Keil *et al.*, 1972a,b, 1973), 0.065–0.214 ppm for blacks of different ages or rural locations (Arthur, 1976), and 0.108 and 0.105 ppm for males and females in four rural communities in the Mississippi Delta (unpublished result from CDC). Thus, there is no evidence that DDT and related compounds downstream from a former DDT factory led to greater absorption than occurred in other places.

**Storage in Other Tissues** With the exception of concentrations of 19–36 ppm in heart, kidney, and liver of a man who died of DDT poisoning under unstated circumstances (Luis, 1952), no information is available on tissue levels in people with heavy exposure, whether occupational or otherwise. Storage of DDT and related compounds in the organs of adults and fetuses in the general population was discussed and tabulated

by Hayes (1975). Concentrations in the viscera of adults averaged 1.0 ppm, but concentrations in lymph nodes and especially bone marrow (a fatty tissue) approached the level in adipose tissue ( $\leq 6.0$ ). Concentrations in some viscera of still-born infants were similar to those in adipose tissue of the same infants and also in adults, suggesting that there had been a mobilization of DDT from fat prior to death.

Saxena *et al.* (1987a) have reported that the levels of DDT in human leiomyomatous uterine tissue were much higher than those in normal tissue (means of 0.845 ppm and 0.103 ppm, respectively). Whether this is related to any estrogenic actions of DDT is unknown.

**Secretion in Milk** No information is available on the secretion of DDT in the milk of women who were occupationally exposed to the compound or who were made ill by it, regardless of circumstances. The concentrations of DDT in the milk of women in various general populations are shown in Table 15.14. As may be seen, values reported from Guatemala and early values from the USSR were much higher than those from other countries, and yet there was no indication of illness among babies fed such milk. The significance of DDT in milk and the dosages that different concentrations of it determine were discussed by Hayes (1975), Jensen (1983), Spindler (1983), and Coulston (1985).

Quinby *et al.* (1965a,b) noted that women apparently were in negative DDT balance during lactation, but no direct measurement of DDT intake of women participating in the study was made. More recently, the ingestion of DDT in food and the secretion of DDT in milk were measured in the same women, and the fact of negative balance was confirmed (Adamovic and Sokic, 1973; Adamovic *et al.*, 1978; Cocisiu *et al.*, 1976). In fact, it has been suggested that this phenomenon may be a



**Table 15.13**  
Concentrations of Some Chlorinated Hydrocarbon Pesticides in Blood of the General Population of Different Countries

| Country              | Year      | Number of samples  | Total DDT (ppm) | Total BHC (ppm) | Dieldrin (ppm) | Heptachlor epoxide (ppm) | References                             |
|----------------------|-----------|--------------------|-----------------|-----------------|----------------|--------------------------|--|
| <b>North America</b> |           |                    |                 |                 |                |                          |  |
| Canada               |           |                    | 0.032           |                 |                |                          | Brown and Chow (1975)                  |
| United States        | 1965      | 10                 | 0.0418          | 0.0034          | 0.0019         | 0.0011                   | Dale <i>et al.</i> (1966a)             |
| USA                  | 1966      | 10, F <sup>a</sup> | 0.0360          |                 |                |                          | Dale <i>et al.</i> (1967)              |
|                      | 1966      | 10, M <sup>a</sup> | 0.0746          |                 |                |                          | Dale <i>et al.</i> (1967)              |
|                      | 1966–1967 | 53 <sup>b</sup>    | 0.00501         | 0.00048         | 0.00026        | 0.00021                  | Selby <i>et al.</i> (1969)             |
|                      | 1967      | 64                 | 0.01425         | 0.00150         | 0.00069        | 0.00000                  | A. Yobs, personal communication (1969) |
|                      | 1968      | 106                | 0.01397         | 0.00000         | 0.00014        | 0.00000                  | A. Yobs, personal communication (1969) |
|                      | 1967–1986 | 1000               | 0.0294          | 0.0021          | 0.0005         | 0.00007                  | Watson <i>et al.</i> (1970)            |
| (rural black)        | 1968      | 139                | 0.0109          |                 | 0.0002         |                          | Finklea <i>et al.</i> (1972)           |
| (urban black)        | 1968      | 175                | 0.0125          |                 | 0.0002         |                          | Finklea <i>et al.</i> (1972)           |
| (rural white)        | 1968      | 210                | 0.0056          |                 | 0.0004         |                          | Finklea <i>et al.</i> (1972)           |
| (urban white)        | 1968      | 199                | 0.0047          |                 | 0.0003         |                          | Finklea <i>et al.</i> (1972)           |
|                      | 1969      | 30 <sup>c,d</sup>  | 0.0144          | 0.0030          | 0.0007         | 0.0011                   | Curley <i>et al.</i> (1969)            |
|                      | 1968      | 5 <sup>e</sup>     | 0.0050          | 0.0012          | 0.0009         | 0.0008                   | Curley and Kimbrough (1969)            |
|                      | 1968      | 10 <sup>e</sup>    | 0.0205          | 0.0034          | 0.0003         | 0.0006                   | Curley and Kimbrough (1969)            |
|                      | 1970      | 26                 | 0.03169         |                 | 0.00149        |                          | Radomski <i>et al.</i> (1971)          |
|                      | 1972      | 214 <sup>f</sup>   | 0.006–0.822     | 0.001–0.017     | 0.001–0.025    |                          | Griffith and Blanke (1975)             |
|                      | 1970s     | 33, F              | 0–0.0782        | 0–0.0058        | 0.001          |                          | Barquet <i>et al.</i> (1981)           |
| (Alaska)             | 1972      | 38 <sup>j</sup>    | 0.002           |                 | 0.011          |                          | Serat <i>et al.</i> (1977)             |
| (urban)              | 1968–1970 | 275, M             | 0.0314          |                 | 0.0003         |                          | Bloomer <i>et al.</i> (1977)           |
| (urban)              | 1968–1970 | 205, F             | 0.0232          |                 | 0.00015        |                          | Bloomer <i>et al.</i> (1977)           |
| (rural)              | 1968–1970 | 232, M             | 0.0357          |                 | 0.0003         |                          | Bloomer <i>et al.</i> (1977)           |
| (rural)              | 1968–1970 | 243, F             | 0.0261          |                 | 0.00011        |                          | Bloomer <i>et al.</i> (1977)           |
| (black) <sup>d</sup> | 1972–1973 | 209                | 0.007–0.292     | 0–0.009         | 0–0.003        | 0–0.003                  | D'Ercole <i>et al.</i> (1976)          |
| (black) <sup>e</sup> | 1972–1973 | 209                | 0.016–0.303     | 0–0.019         | 0–0.003        | 0–0.001                  | D'Ercole <i>et al.</i> (1976)          |
| (white) <sup>d</sup> | 1972–1973 | 130                | 0.003–0.056     | 0–0.009         | 0–0.002        | 0–0.002                  | D'Ercole <i>et al.</i> (1976)          |
| (white) <sup>e</sup> | 1972–1973 | 130                | 0.007–0.160     | 0–0.009         | 0–0.006        | 0–0.002                  | D'Ercole <i>et al.</i> (1976)          |
|                      | 1976–1980 | 3127               | 0.090           | 0.0002          | 0.0001         |                          | HANES II (1980)                        |
| (South Carolina)     | 1978      | 25                 |                 |                 | 0–0.0034       |                          | Sandifer <i>et al.</i> (1981)          |
| (Hawaii)             | 1979      | 200                | 0.004–0.152     | 0–0.0002        | 0–0.002        |                          | Takahashi and Parks (1982)             |
|                      | 1980      | 499                | 0.001–2.821     |                 |                |                          | Kreiss <i>et al.</i> (1981)            |
| <b>South America</b> |           |                    |                 |                 |                |                          |  |
| Argentina            | 1970      | 20 <sup>g</sup>    | 0.01934         | 0.02399         | 0.00143        |                          | Radomski <i>et al.</i> (1971)          |
|                      | 1970      | 18 <sup>h</sup>    | 0.01327         | 0.00704         | 0.00094        |                          | Radomski <i>et al.</i> (1971)          |
|                      | 1970      | 19 <sup>i</sup>    | 0.00869         | 0.00704         | 0.00054        |                          | Radomski <i>et al.</i> (1971)          |
| Brazil               | 1975      | 32, F              | 0.036           |                 |                |                          | Procianoy and Schvartsman (1982)       |
|                      | 1975?     | 32 <sup>d</sup>    | 0.0153          |                 |                |                          | Procianoy and Schvartsman (1982)       |
| (industrial)         | 1980?     | 21                 | 0.0219          | 0.0090          |                |                          | de Fernicola and de Azevedo (1982)     |
| (rural)              | 1980?     | 21                 | 0.0316          | 0.0087          |                |                          | de Fernicola and de Azevedo (1982)     |
| <b>Europe</b>        |           |                    |                 |                 |                |                          |  |
| Hungary              | 1967–1968 | 120                | 0.034           | 0.019           | 0.001          |                          | Czegledi-Janko (1969)                  |
| Norway               | 1981–1982 | 15 <sup>e</sup>    | 0.019           | 0.001           |                |                          | Skaare <i>et al.</i> (1988)            |
| (immigrants)         | 1981–1982 | 5 <sup>e</sup>     | 0.150           | 0.002           |                |                          | Skaare <i>et al.</i> (1988)            |
| Poland               |           |                    | 0.172, F        | 0.008, F        |                |                          | Jonczyk (1970)                         |
|                      | 1972      | 15                 | 0.030           | 0.084           |                |                          | Bojanowska <i>et al.</i> (1973)        |
|                      | 1979      | 100                | 0.0281          | 0.0092          |                |                          | Syrowatka <i>et al.</i> (1979)         |
|                      |           | 13                 | 0.0209          | 0.0038          | 0.0014         |                          | Zimmerli and Marek (1973)              |
| Switzerland          |           |                    | 0.07478         | 0.00734         |                |                          | Reiner <i>et al.</i> (1977)            |
| Yugoslavia           | 1975      | 147                | 0.0353          |                 |                |                          | Krauthacker <i>et al.</i> (1980b)      |
| (urban)              | 1978–1979 | 11                 | 0.0102          |                 |                |                          | Krauthacker <i>et al.</i> (1980a)      |
| (rural)              | 1979      | 41                 | 0.0162          | 0.0035          |                |                          | Roncevic <i>et al.</i> (1987)          |
|                      | 1980s     | 14, F              | 0.0215          | 0.0059          |                |                          | Bazulic <i>et al.</i> (1984)           |
|                      | 1978–1981 | 31, F              |                 |                 |                |                          |  |

(continued)



Table 15.13 (Continued)

| Country   | Year      | Number of samples | Total DDT (ppm) | Total BHC (ppm) | Dieldrin (ppm) | Heptachlor epoxide (ppm) | References                      |
|-----------|-----------|-------------------|-----------------|-----------------|----------------|--------------------------|---------------------------------|
| Africa    |           |                   |                 |                 |                |                          |                                 |
| Tunisia   | 1980s     | 20                | 0.091           | 0.007           |                |                          | Jemma <i>et al.</i> (1986)      |
| Asia      |           |                   |                 |                 |                |                          |                                 |
| India     |           |                   |                 |                 |                |                          |                                 |
| (Delhi)   | 1985?     | 50                | 0.301           |                 |                |                          | Saxena <i>et al.</i> (1987b)    |
| (Lucknow) | 1981?     | 48, M             | 0.028           | 0.075           |                |                          | Kaphalia and Seth (1983)        |
| (Lucknow) | 1979–1980 | 29 <sup>e</sup>   | 0.026           | 0.0499          |                |                          | Saxena <i>et al.</i> (1983)     |
| (Lucknow) | 1970s     | 25 <sup>e</sup>   | 0.020           | 0.022           |                |                          | Siddiqui <i>et al.</i> (1981)   |
| Israel    | 1975      | 19                | 0.0740          | 0.0147          | 0.0099         | 0.0136                   | Polishuk <i>et al.</i> (1977)   |
|           | 1984–1985 | 14, M             | 0.0249          |                 | 0.0027         | 0.0116                   | Pines <i>et al.</i> (1987)      |
| Japan     | 1970      | 10                | 0.074           | 0.150           |                |                          | Tokutsu <i>et al.</i> (1970)    |
|           | 1971      |                   | 0.005           | 0.006           | 0.001          |                          | Kojima <i>et al.</i> (1971)     |
|           | 1971      | 138               | 0.0183          |                 |                |                          | Kasai <i>et al.</i> (1972)      |
|           | 1971      |                   | 0.0093          | 0.191           | 0.0030         |                          | Yamagishi <i>et al.</i> (1972a) |
|           | 1971      |                   | 0.0285          | 0.0577          |                |                          | Kaku (1973)                     |
|           | 1972      |                   | 0.001–0.078     | 0.030–0.067     | 0.003          |                          | Study Group (1972)              |
|           |           | 37                | 0.0437, F       | 0.030–0.046     | 0–0.0031       |                          | Nawa (1973)                     |
|           |           | <sup>e</sup>      | 0.1358          | 0.0326          |                |                          | Hara <i>et al.</i> (1973)       |
|           |           | <sup>d</sup>      | 0.0210          | 0.0185          |                |                          | Hara <i>et al.</i> (1973)       |
|           |           | 17                |                 | 0.0118          |                |                          | Inoue <i>et al.</i> (1974)      |
|           | 1973      | 82                | 0.0179          | 0.0106          | 0.0011         |                          | Abe <i>et al.</i> (1974)        |
| Oceania   |           |                   |                 |                 |                |                          |                                 |
| Australia |           | 52                | 0.0172          | 0.0032          | 0.0023         | 0.0031                   | Siyali (1972)                   |
|           |           | 47                | 0.0167          |                 |                |                          | Ouw and Shandar (1974)          |

<sup>a</sup> F, Female; M, male.<sup>b</sup> Geometric mean.<sup>c</sup> Mean of positive values only.<sup>d</sup> Cord blood from live term infants.<sup>e</sup> Maternal blood.<sup>f</sup> Ages 41–60.<sup>g</sup> Adults.<sup>h</sup> 6–11 years old.<sup>i</sup> 1–5 years old.<sup>j</sup> 6–17-year-old Eskimos.

significant factor in determining the lower levels of DDT found in women than men in the general population (Adamovic and Sokic, 1973).

Johnsson *et al.* (1977) found significantly lower levels of DDT (mean of 0.008 ppm) and of DDE (mean of 0.035 ppm) than had been reported earlier for the milk of city dwellers. However, levels remained quite high (0.05–1.90 ppm) in some rural black people (Woodard *et al.*, 1976). Some evidence suggests that DDT levels are higher in milk from smokers than nonsmokers, although there may be an occupational explanation (Coulston, 1985).

Overall, despite the presence of DDT in human milk and placenta, there seems little risk to neonates in many different populations.

**Excretion of DDT-Related Compounds** Among workers whose DDT intake was estimated to be about 35 mg/day, Ortelee (1958) reported that the concentration of DDA in urine ranged from 0.12 to 7.56 ppm and averaged 1.71 ppm. Among workers whose exposure was about half as great, Laws *et al.*

(1967) found concentrations from 0.01 to 2.67 ppm with a mean of 0.97 ppm.

Continuous sampling of a DDT-formulating plant worker's urine showed that excretion of DDA increased promptly when exposure began on each of 5 consecutive workdays but often continued after exposure, sometimes reached a peak about midnight, and then decreased rapidly. On day 6, when there was no occupational exposure to DDT, the excretion of DDA continued until a very low level was reached. The highest concentration of DDA reported in this study was 0.68 ppm (Wolfe and Armstrong, 1971).

The urine of people in the general population contains not only DDA but also neutral compounds; the average concentrations reported by Cueto and Biros (1967) were: *p,p'*-DDT, 0.0007 ppm and *p,p'*-DDE, 0.0156 pm. Men with heavy occupational exposure to DDT excreted much more DDA but showed only a statistically insignificant increase in excretion of DDT and DDE.

The values just given for the average excretion of DDA, DDT, and DDE by different, small groups of people would



**Table 15.14**  
Concentrations of Some Chlorinated Hydrocarbon Pesticides in Milk of the General Population of Different Countries

| Country                    | Year      | Number of samples | Total DDT (ppm)    | Total BHC (ppm)    | Dieldrin (ppm)     | Heptachlor epoxide (ppm) | References                          |
|----------------------------|-----------|-------------------|--------------------|--------------------|--------------------|--------------------------|-------------------------------------|
| North America              |           |                   |                    |                    |                    |                          |                                     |
|                            |           |                   |                    |                    |                    |                          |                                     |
| Canada                     | 1967-1968 | 147               | 0.139              |                    | 0.005              | 0.003                    | Ritchey <i>et al.</i> (1972)        |
|                            | unknown   | 15                | 0.019-0.035        |                    |                    |                          | Musial <i>et al.</i> (1974)         |
|                            | unknown   |                   |                    |                    | 0.009              | 0.003                    | Larsen <i>et al.</i> (1971)         |
|                            | unknown   |                   |                    |                    | 0.013              | 0.052                    | Larsen <i>et al.</i> (1971)         |
|                            | 1969-1974 | 101               |                    |                    |                    |                          |                                     |
|                            | 1970      | 90                | 0.077              | 0.002              | 0.005              | 0.004                    | Mes <i>et al.</i> (1977)            |
|                            | 1975      | 100               | 0.046              | 0.002              | 0.002              | 0.001                    | Mes and Davies (1979)               |
|                            | 1978-1979 | 154               | 0.039              |                    |                    |                          | Dillon <i>et al.</i> (1981)         |
|                            | 1982      | 210               | 0.038              | 0.008              | 0.002              |                          | Collins <i>et al.</i> (1982)        |
|                            | 1986?     | 18                | 0.016              | 0.006              | 0.0004             | 0.0002                   | Davies and Mes (1987)               |
| United States              | 1950      | 32                | 0.13               |                    |                    |                          | Laug <i>et al.</i> (1951)           |
|                            | 1960-1961 | 10                | 0.12               |                    |                    |                          | Quinby <i>et al.</i> (1965b)        |
|                            | 1962      | 6                 | 0.37 <sup>a</sup>  |                    |                    |                          | West (1964)                         |
|                            | 1968      | unknown           | 0.078              |                    |                    |                          | Curley and Kimbrough (1969)         |
|                            | 1970      | 53                | 0.101              |                    |                    | 0.0066                   | Kroger (1972)                       |
|                            | 1970-1971 | 101               | 0.17               |                    |                    |                          | Wilson <i>et al.</i> (1973)         |
|                            | 1975      | 55                | 0.114              |                    |                    |                          | Bradt and Herrenkohl (1976)         |
|                            | 1973-1974 | 57                | 0.344              | 0.005              | 0.004              | 0.004                    | Strassman and Kutz (1977)           |
|                            | 1971-1972 | 40                | 0.126              |                    |                    |                          | Savage <i>et al.</i> (1973)         |
| (black)                    | 1974      | 38                | 0.447              |                    |                    |                          | Woodard <i>et al.</i> (1976)        |
| (white)                    | 1974      | 14                | 0.075              |                    |                    |                          | Woodard <i>et al.</i> (1976)        |
| (total)                    | 1975      | 1436              | 0.070              | 0.003              | 0.002              | 0.001                    | Savage <i>et al.</i> (1981)         |
| (pesticide work-ers)       | 1973-1975 | 34                | 0.719              | 0.022              | 0.006              | 0.003                    | Barnett <i>et al.</i> (1979)        |
| (non-pesticide workers)    | 1973-1975 | 6                 | 0.083              | 0.011              | 0.004              | 0.002                    | Barnett <i>et al.</i> (1979)        |
| (Hawaii)                   | 1979-1980 | 54                | 2.16 <sup>b</sup>  | 0.180 <sup>b</sup> | 0.042 <sup>b</sup> | 0.036 <sup>b</sup>       | Takei <i>et al.</i> (1983)          |
| (Missouri)                 | 1977      | 51                | 0.022              | 0.003              | 0.014              |                          | Jonsson <i>et al.</i> (1977)        |
| Central America and Mexico |           |                   |                    |                    |                    |                          |                                     |
|                            |           |                   |                    |                    |                    |                          |                                     |
| El Salvador                | 1973-1974 | 40                | 0.695              | 0.012              | 0.005              | 0.003                    | de Campos and Olszyna-Marzys (1978) |
| Guatemala                  |           |                   |                    |                    |                    |                          |                                     |
|                            |           |                   |                    |                    |                    |                          |                                     |
| (La Bomba)                 | 1970      | 10                | 2.15               | 0.03               | trace              | 0.003                    | Olszyna-Marzys <i>et al.</i> (1973) |
| (El Rosario)               | 1970      | 27                | 1.84               | 0.007              | 0.002              | 0.007                    | Olszyna-Marzys <i>et al.</i> (1973) |
| (Cerro Colorado)           | 1971      | 9                 | 4.07               | 0.02               |                    | trace                    | Olszyna-Marzys <i>et al.</i> (1973) |
| (City)                     | 1974      | 15                | 0.480              |                    |                    |                          | de Campos and Olszyna-Marzys (1978) |
|                            |           |                   |                    |                    | 0.005              | 0.002                    | de Campos and Olszyna-Marzys (1978) |
| (Izabal)                   | 1974      | 10                | 2.55               |                    |                    |                          | de Campos and Olszyna-Marzys (1978) |
|                            |           |                   |                    |                    | 0.070              | 0.003                    | de Campos and Olszyna-Marzys (1978) |
| (Escuintla)                | 1974      | 10                | 3.54               |                    |                    |                          | Albert <i>et al.</i> (1981)         |
|                            |           |                   |                    |                    | 0.030              |                          |                                     |
| Mexico                     | 1976      | 15                | 0.266              |                    |                    |                          |                                     |
| South America              |           |                   |                    |                    |                    |                          |                                     |
|                            |           |                   |                    |                    |                    |                          |                                     |
| Argentina                  | 1981      | 20                | 0.061              | 0.037              |                    |                          | Landoui and Astolfi (1982)          |
| Chile                      | 1977      | unknown           | 0.258              |                    |                    |                          | Albert (1981)                       |
| Brazil                     | 1975-1976 | 26                | 0.090              |                    |                    |                          | Matuo <i>et al.</i> (1980)          |
| Uruguay                    |           | 10                | 0.230              | 0.057              | 0.032              | 0.002                    | Bauza (1975)                        |
| Europe                     |           |                   |                    |                    |                    |                          |                                     |
|                            |           |                   |                    |                    |                    |                          |                                     |
| Austria                    |           |                   |                    |                    |                    |                          | Pesendorfer (1975)                  |
| (Vienna)                   |           | 22                | 4.725 <sup>b</sup> | 1.488 <sup>b</sup> |                    |                          | Pesendorfer (1975)                  |
| (Mistelbach)               |           | 9                 | 6.13 <sup>b</sup>  | 4.013 <sup>b</sup> |                    |                          | Heyndrickx and Maes (1969)          |
| Belgium                    | 1968      | 20                | 0.128              | 0.010              | 0.004              |                          | Rogirst <i>et al.</i> (1983)        |
|                            | 1982      | 47                | 0.041              | 0.0567             |                    | 0.0021                   | Hruska (1969)                       |
|                            |           |                   | 0.101              |                    |                    |                          | Suvak (1970)                        |
| Czechoslovakia             | 1968      | unknown           | 0.209              |                    |                    |                          | Andersen and Orbaek (1982)          |
|                            |           | 393               | 1.15 <sup>b</sup>  | 0.08 <sup>b</sup>  | 0.04 <sup>b</sup>  |                          | Egan <i>et al.</i> (1965)           |
| Denmark                    | 1982      | 57                | 0.013              | 0.006              |                    |                          | Collins <i>et al.</i> (1982)        |
| England                    | 1963-1964 | 19                | 0.051              | 0.008              | 0.002              |                          | Wickström <i>et al.</i> (1983)      |
| United Kingdom             | 1979-1980 | 102               | 0.031              |                    |                    |                          |                                     |
| Finland                    | 1982      | 50                |                    |                    |                    |                          |                                     |

(continued)



Table 15.14 (Continued)

| Country        | Year      | Number of samples | Total DDT (ppm)        | Total BHC (ppm)    | Dieldrin (ppm)     | Heptachlor epoxide (ppm) | References                                |
|----------------|-----------|-------------------|------------------------|--------------------|--------------------|--------------------------|---|
| France         |           | 59 <sup>c</sup>   |                        | 0-0.190            | 0.007-0.032        | 0.002-0.012              | Luquet <i>et al.</i> (1972)               |
|                | 1971-1972 |                   | 3.24 <sup>b</sup>      | 2.75 <sup>b</sup>  | 0.23 <sup>b</sup>  | 0.28 <sup>b</sup>        | Luquet <i>et al.</i> (1974a)              |
|                | 1972-1973 |                   | 3.51 <sup>b</sup>      | 1.77 <sup>b</sup>  |                    | 0.28 <sup>b</sup>        | Luquet <i>et al.</i> (1974b)              |
|                | 1970      | 49                |                        | 0.003-0.202        | 0.001              | 0.001                    | Goursaud <i>et al.</i> (1971)             |
|                | 1974-1975 | 13                | 1.04 <sup>b</sup>      | 0.052 <sup>b</sup> | 0.035 <sup>b</sup> | 0.08 <sup>b</sup>        | De Bellini <i>et al.</i> (1977)           |
| Germany (West) | 1970?     | 43                | 0.121                  |                    |                    |                          | Acker and Shulte (1970)                   |
| Germany        | 1970?     |                   | 0.569                  |                    |                    |                          | Adamovic <i>et al.</i> (1971)             |
|                | 1969      | 57                | 0.23                   |                    |                    |                          | Engst and Knoll (1972)                    |
|                | 1970      | 18                | 0.16                   |                    |                    |                          | Engst and Knoll (1972)                    |
|                | 1971      | 96                | 0.32                   |                    |                    |                          | Knoll and Jayaraman (1973a,b)             |
|                | 1970      |                   | 4.1 <sup>b</sup>       | 0.54 <sup>b</sup>  |                    |                          | Acker and Shulte (1971)                   |
|                | 1970      |                   |                        |                    |                    |                          | Acker and Shulte (1971)                   |
|                | 1973      | 184               | 0.23                   |                    |                    |                          | Thielemann <i>et al.</i> (1975)           |
| Germany (East) | 1978      | 85                | 0.349                  |                    |                    |                          | Thielemann (1979)                         |
|                | 1979      | 200               | 0.096                  | 0.010              |                    |                          | Hesse <i>et al.</i> (1981)                |
| Germany (West) | 1979-1980 | unknown           | 2.00 <sup>b</sup>      |                    |                    |                          | Acker (1981)                              |
| Hungary        | 1963      | 10                | 0.13-0.26 <sup>d</sup> |                    |                    |                          | Denes (1964)                              |
| Ireland        | 1971-1972 |                   | 0.128 <sup>b</sup>     | 0.001 <sup>b</sup> | 0.001 <sup>b</sup> | 0.005 <sup>b</sup>       | Downey <i>et al.</i> (1975)               |
| Italy          | 1983-1985 | 65                | 0.051                  | 0.007              |                    |                          | Dommarco <i>et al.</i> (1987)             |
| Netherlands    | 1969      | 50                | 2.7 <sup>b</sup>       |                    |                    |                          | Tuinstra (1971)                           |
|                | 1978?     | 69                | 0.031                  |                    | 0.0023             |                          | Eckenhansen <i>et al.</i> (1981)          |
| Norway         | 1976      | 45                | 0.050                  |                    |                    |                          | Brevik and Bjerk (1978)                   |
|                | 1979      | 19                | 0.024                  |                    |                    |                          | Skaare (1981)                             |
|                | 1982      | 34                | 0.024                  | 0.002              |                    |                          | Skaare <i>et al.</i> (1988)               |
| (immigrants)   | 1982      | 5                 | 0.107                  | 0.008              |                    |                          | Skaare <i>et al.</i> (1988)               |
| Poland         |           | 128               | 0.25                   | 0.003              |                    |                          | Juskiewicz <i>et al.</i> (1972)           |
|                | 1966      | 26                | 0.27                   |                    |                    |                          | Bronisz and Ochynski (1968)               |
|                | 1967      | 25                | 0.40                   |                    |                    |                          | Bronisz and Ochynski (1968)               |
|                | 1970?     | 40                | 0.28                   | 0.006              |                    |                          | Kontek <i>et al.</i> (1971)               |
|                | 1979      | 40                | 0.179                  |                    |                    |                          | Kontek <i>et al.</i> (1981)               |
| Portugal       | 1972      | 168               | 0.326                  |                    |                    |                          | Graca <i>et al.</i> (1974)                |
| Romania        | 1968?     | 100               | 0.08-1.58              | 0.08-1.58          |                    |                          | Unterman and Sirghie (1969)               |
|                |           |                   |                        |                    |                    |                          | Mandroui and Iordachescu (1971)           |
| Spain          | 1979      | 45                | 0.181                  | 0.039              | 0.0005             |                          | Pozo Lora <i>et al.</i> (1979)            |
|                | 1981      | 20                | 0.256                  | 0.020              | 0.003              | 0.004                    | Baluja <i>et al.</i> (1982)               |
| Sweden         | 1967?     | unknown           | 0.117                  |                    |                    |                          | Lofroth (1968)                            |
|                | 1967-1969 | 22                | 0.115                  | traces             | 0.001              |                          | Westoo <i>et al.</i> (1970)               |
|                | 1976-1977 | ?                 | 0.033                  |                    | 0.0007             |                          | Westoo and Noren (1978)                   |
|                | 1978-1979 | 23                | 0.061                  | 0.0036             | 0.0008             |                          | Hofvander <i>et al.</i> (1981)            |
| USSR           | 1964      | 16                | 1.22-4.88              |                    |                    |                          | Damaskin (1965)                           |
|                | 1964-1965 | 4505              | 0.1-1.0                |                    |                    |                          | Gracheva (1969)                           |
|                | 1969?     | 680               | 0.25                   |                    |                    |                          | Gracheva (1970)                           |
|                | 1967      | 370               | 0.1                    |                    |                    |                          | Komarova (1970)                           |
|                | 1977?     | 252               | 0.580                  |                    |                    |                          | Gulko <i>et al.</i> (1978)                |
| Yugoslavia     | 1981-1982 | 50                | 0.0743                 | 0.011              |                    |                          | Krauthacker <i>et al.</i> (1986)          |
|                | 1977      | 34                | 0.051                  |                    |                    |                          | Krauthacker <i>et al.</i> (1980)          |
| Africa         |           |                   |                        |                    |                    |                          |   |
| Kenya          |           |                   |                        |                    |                    |                          |   |
| (nomads)       | 1984      | 13                | 1.69 <sup>b</sup>      | 0.038 <sup>b</sup> | 2.445 <sup>b</sup> |                          | Kanja <i>et al.</i> (1986)                |
| (farmers)      | 1985      | 48                | 9.76 <sup>b</sup>      | 0.22 <sup>b</sup>  | 0.310 <sup>b</sup> |                          | Kanja <i>et al.</i> (1986)                |
| Nigeria        | 1981-1982 | 35                | 1.51 <sup>b</sup>      | 0.52 <sup>b</sup>  |                    |                          | Atuma and Vaz (1986)                      |
| Tunisia        | 1980s     | 80                | 0.145                  | 0.039              | 0.006              |                          | Jamma <i>et al.</i> (1986)                |
| Asia           |           |                   |                        |                    |                    |                          |   |
| India          |           |                   |                        |                    |                    |                          |   |
| (Lucknow)      | 1970s     | 25                | 0.12                   | 0.107              |                    |                          | Siddiqui <i>et al.</i> (1981)             |
| (Punjab)       | 1979      | 75                | 0.51                   | 0.195              |                    |                          | Kalra and Chawla (1981)                   |
| (Bangalore)    | unknown   | 6                 | 0.053                  | 0.014              |                    |                          | Ramakrishnan <i>et al.</i> (1985)         |
| (Calcutta)     | unknown   | 6                 | 0.114                  | 0.031              |                    |                          | Ramakrishnan <i>et al.</i> (1985)         |
| (Bombay)       | unknown   | 6                 | 0.224                  | 0.053              |                    |                          | Ramakrishnan <i>et al.</i> (1985)         |
| (Ahmedabad)    | 1981-1982 | 50                | 0.305                  | 0.225              |                    |                          | Jani <i>et al.</i> (1988)                 |
| Iran           | 1974-1976 | 131               | 0.044                  | 0.008              | 0.011              |                          | Hashemy-Tonkabony and Fateminassab (1977) |

(continued)



Table 15.14 (Continued)

| Country          | Year      | Number of samples | Total DDT (ppm)    | Total BHC (ppm)    | Dieldrin (ppm)     | Heptachlor epoxide (ppm) | References                           |
|------------------|-----------|-------------------|--------------------|--------------------|--------------------|--------------------------|--------------------------------------|
| Iraq             | 1983–1984 | 50                | 0.145              | 0.073              | 0.030              |                          | Al-Omar <i>et al.</i> (1985)         |
| Israel           | 1975      | 29                | 0.0717             | 0.0101             | 0.0070             | 0.0091                   | Polishuk <i>et al.</i> (1977)        |
|                  | 1980s     | 100               | 0.0875             | 0.0125             |                    |                          | Weisenberg <i>et al.</i> (1985)      |
| Japan            | 1970–1971 |                   |                    | 0.02–0.4           |                    |                          | Narafu (1971)                        |
|                  | 1971–1972 | 398               | 0.0562             |                    |                    |                          | Anonymous (1972)                     |
|                  | 1971      | 43                | 0.179              |                    |                    |                          | Hidaka <i>et al.</i> (1972)          |
|                  | 1970      | 10                | 0.071              |                    |                    |                          | Tokutsu <i>et al.</i> (1970)         |
|                  | 1970?     | 5                 | 0.160              |                    |                    |                          | Takeshita and Inuyama (1970)         |
|                  | 1970?     | 10                | 0.120              |                    |                    |                          | Takeshita and Inuyama (1970)         |
|                  | 1971?     |                   | 0.04               |                    |                    |                          | Kojima <i>et al.</i> (1971)          |
|                  | 1971?     | 59                | 0.019–0.105        |                    |                    |                          | Kato <i>et al.</i> (1971)            |
|                  | 1971?     | 14                | 0.047              |                    |                    |                          | Sugaya <i>et al.</i> (1971)          |
|                  | 1971      | 454               | 0.179              | 0.033–0.44         |                    |                          | Hayashi (1972a,b); Study Group, 1972 |
|                  | 1971–1972 | 398               | 0.056              |                    |                    |                          | Anonymous (1972)                     |
|                  | 1971      |                   | 0.044              |                    |                    |                          | Yamagishi <i>et al.</i> (1972a)      |
|                  |           | 30                | 2.0 <sup>b</sup>   |                    |                    |                          | Mizoguchi <i>et al.</i> (1972)       |
|                  |           | 54                | 0.025              |                    |                    |                          | Taira <i>et al.</i> (1972)           |
|                  | 1971–1972 | 398               | 0.0626             | 0.105              | 0.0034             | 0.0011                   | Hayashi (1972a,b)                    |
|                  | 1971–1972 | 5                 | 0.027              |                    |                    |                          | Nagai (1972)                         |
|                  | 1971–1972 | 5                 | 0.037              |                    |                    |                          | Nagai (1972)                         |
|                  | 1971–1972 | 5                 | 0.016              |                    |                    |                          | Nagai (1972)                         |
|                  | 1971–1972 | 5                 | 0.037              |                    |                    |                          | Nagai (1972)                         |
|                  |           | 30                | 0.033              |                    |                    |                          | Oura <i>et al.</i> (1972)            |
|                  | 1971–1972 | 123               | 0.105              |                    |                    |                          | Kawai <i>et al.</i> (1973)           |
|                  | 1971–1972 |                   | 0.038–0.075        |                    |                    |                          | Kamata (1973)                        |
|                  | 1970      |                   | 3.780 <sup>b</sup> |                    |                    |                          | Suzuki <i>et al.</i> (1973)          |
|                  | 1971      |                   | 3.592 <sup>b</sup> |                    |                    |                          | Suzuki <i>et al.</i> (1973)          |
|                  | 1972      |                   | 3.822 <sup>b</sup> |                    |                    |                          | Suzuki <i>et al.</i> (1973)          |
|                  | 1973      |                   | 0.0854             |                    |                    |                          | Kamata (1974)                        |
|                  | 1971–1975 |                   | 0.172              | 0.385              | 0.006              |                          | Matsunaga <i>et al.</i> (1975)       |
|                  |           | 26                | 0.061              | 0.067              |                    |                          | Anonymous (1975)                     |
|                  | 1971–1972 | 398               | 0.0626             | 0.1009             | 0.0034             |                          | Hayashi (1973, 1974)                 |
|                  |           | 10                | 0.981              |                    | 0.0051             |                          | Inuyama and Takashita (1973)         |
|                  |           | 10                |                    | 0.071              |                    |                          |                                      |
|                  | 1973      | 7                 | 0.071              | 0.109              | 0.002              |                          | Shimamoto <i>et al.</i> (1973)       |
|                  | 1974      |                   | 2.436 <sup>b</sup> | 2.313 <sup>b</sup> |                    |                          | Sugaya <i>et al.</i> (1976)          |
|                  |           |                   | 2.353 <sup>b</sup> | 2.442 <sup>b</sup> | 0.254 <sup>b</sup> |                          | Suzuki <i>et al.</i> (1976)          |
|                  |           | 10                | 0.234              | 0.040              | not found          | not found                | Yamada and Sakamoto (1973)           |
|                  |           | 20                | 1.89 <sup>b</sup>  |                    | 0.052 <sup>b</sup> |                          | Yakushiji <i>et al.</i> (1979)       |
| Turkey           |           |                   |                    |                    |                    |                          | Karakaya <i>et al.</i> (1987)        |
| (Ankara)         | 1984–1985 | 61                | 3.66 <sup>b</sup>  | 0.97 <sup>b</sup>  |                    |                          | Karakaya <i>et al.</i> (1987)        |
| (Adana-Cujurova) | 1984–1985 | 52                | 10.57 <sup>b</sup> | 1.45 <sup>b</sup>  |                    |                          |                                      |
| Oceania          |           |                   |                    |                    |                    |                          |                                      |
| Australia        | 1970      | 67                | 0.014 <sup>e</sup> |                    |                    |                          | Newton and Greene (1972)             |
|                  | 1970      | 67                | 0.007 <sup>f</sup> |                    |                    |                          | Newton and Greene (1972)             |
|                  | 1970      | 67                | 0.066 <sup>g</sup> |                    |                    |                          | Newton and Greene (1972)             |
| (Brisbane)       | 1971–1972 | 20                | 0.288              |                    |                    |                          | Miller and Fox (1973)                |
| (Mareeba)        | 1971–1972 | 20                | 0.415              |                    |                    |                          | Miller and Fox (1973)                |
|                  |           | 45                | 0.064              |                    |                    |                          | Siyali (1972)                        |
|                  |           | 22                | 0.076              |                    |                    |                          | Stacy and Thomas (1975)              |
|                  | 1980      | 14                | 0.042              | 0.001              | 0.013              | 0.004                    | Conway <i>et al.</i> (1985)          |
| (urban)          | 1979–1980 | 45                | 0.046              |                    | 0.009              |                          | Stacey <i>et al.</i> (1985)          |
| (rural)          | 1979–1980 | 95                | 0.041              |                    | 0.008              |                          | Stacey <i>et al.</i> (1985)          |
| New Guinea       | 1972      | 16                | 0.004              |                    |                    |                          | Hornabrook <i>et al.</i> (1972)      |
|                  | 1972      | 19                | 0.015              |                    |                    |                          | Hornabrook <i>et al.</i> (1972)      |

<sup>a</sup> Maximal value.<sup>b</sup> Concentration in milk fat (ppm milk fat).<sup>c</sup> Not all samples tested for all compounds.<sup>d</sup> Range of values for milk containing 4% fat containing 3.3–6.6 ppm.<sup>e</sup> At beginning of feeding, 1.8% fat.<sup>f</sup> At middle of feeding, 1.2% fat.<sup>g</sup> At end of feeding, 5.1% fat.



**Table 15.15**  
Urinary Excretion of DDA by People in the United States with Varying Degrees of Exposure to DDT<sup>a</sup>

| Exposure                           | Year      | Number of samples | DDA excretion (ppm)    |                   | Reference                    |
|------------------------------------|-----------|-------------------|------------------------|-------------------|------------------------------|
|                                    |           |                   | Range                  | Mean              |                              |
| General population                 | 1954      | 8                 | <0.05                  | —                 | Hayes <i>et al.</i> (1956)   |
|                                    | 1957      | 8                 | <0.02–0.07             | —                 | Hayes <i>et al.</i> (1971)   |
|                                    | 1962      | 23                | <0.02–0.18             | —                 | Durham <i>et al.</i> (1965)  |
|                                    | 1968      | 11                | 0.008–0.019            | 0.014             | Cranmer <i>et al.</i> (1969) |
| Environmental <sup>b</sup>         | 1962      | 13                | 0.02–0.11              | —                 | Durham <i>et al.</i> (1965)  |
|                                    | 1962      | 11                | 0.02–0.17              | —                 | Durham <i>et al.</i> (1965)  |
| Applicators                        | 1957      | 40                | 0.12–7.56              | 1.71              | Ortelee (1958)               |
| Formulators                        | 1966      | 35                | <0.01–2.67             | 0.97              | Laws <i>et al.</i> (1967)    |
| Makers and Formulators             | 1953–1954 | 2                 | 0.10–0.42 <sup>c</sup> | 0.21 <sup>b</sup> | Hayes <i>et al.</i> (1956)   |
| Volunteers given 3.5 mg/day orally | 1957–1958 | 6                 | 0.06–1.98 <sup>d</sup> | 0.23 <sup>c</sup> | Hayes <i>et al.</i> (1971)   |
|                                    | 1953–1954 | 6                 | 0.69–9.67 <sup>c</sup> | 2.46 <sup>b</sup> | Hayes <i>et al.</i> (1956)   |
| Volunteers given 35 mg/day orally  | 1957–1958 | 6                 | 0.18–9.21 <sup>d</sup> | 3.09 <sup>c</sup> | Hayes <i>et al.</i> (1971)   |

<sup>a</sup> Slightly modified from Hayes (1966) by permission of the National Academy of Sciences.<sup>b</sup> Residents living within 500 ft of agricultural application.<sup>c</sup> Based on all samples after week 35 of dosage.<sup>d</sup> Based on all samples from week 35 through week 93 after dosage started.

indicate a concentration of 0.0358 ppm of DDT-related material expressed as DDT. Although the DDT intakes of these particular groups were not measured, the urinary excretion is of such an order of magnitude that it may account for the excretion of all the absorbed DDT. The excretion of DDA by people with different kinds and degrees of exposure is presented in Table 15.15.

DDT and DDE are excreted in the bile; the concentrations for five men without special exposure varied as follows: *p,p'*- and *o,p'*-DDT combined, 0.0000–0.0009 ppm and *p,p'*-DDE, 0.0005–0.0056 ppm. Higher levels were found in the bile of one pest-control operator (Paschal *et al.*, 1974).

**Other Laboratory Findings** In the absence of occupational DDT poisoning, there has been no opportunity to explore (as has been done with the cyclodiene insecticides) the relationship between clinical and EEG findings. In fact, the only DDT workers studied in this regard were exposed also to BHC and benzilan, so the findings might have been related to one or more of the compounds or to their interaction. Electroencephalograms were obtained from 73 of these workers exposed for periods ranging from 7 months to 20 years. Just over 78% of the records were normal and 21.9% were abnormal. The most severe changes involved persons exposed to the three compounds for 1–2 years; less severe changes were seen with either shorter or longer exposure. The changes were not correlated with age; the range and mean of age for those judged abnormal were almost identical with these values for persons considered normal. Some of the records showed bitemporal sharp waves with shifting lateralization combined with low-voltage theta activity. Other records showed spike complexes, paroxysmal discharges composed of slow and sharp waves

most pronounced anteriorly, and low-voltage rhythmic spikes posteriorly. None of the persons examined showed any abnormal clinical neurological finding (Israeli and Mayersdorf, 1973; Mayersdorf and Israeli, 1974). The incidence of abnormal electroencephalograms in the general population is 9.0 or 9.2%, according to other investigators cited by Israeli and Mayersdorf. Czeglédi-Janko and Avar (1970) considered that nonspecific EEG abnormalities occur in 10–20% of the general population. Under the circumstances, there is some question of whether the results are meaningful.

Clinical laboratory findings associated with DDT poisoning are not diagnostic.

**Treatment of Poisoning** No useful guidance regarding treatment has been gleaned from the very few cases of DDT poisoning that have occurred. Animal studies indicate that sedatives, ionic calcium, and glucose or another ready source of energy would be useful. On the basis of experience in treating people poisoned by different convulsive poisons, it seems likely that diazepam would be beneficial (see Section 15.2.5).

### 15.3.2 TDE

#### 15.3.2.1 Identity, Properties, and Uses

**Chemical Name** TDE is 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane.

**Structure** See Table 15.2.

**Synonyms** The common name TDE (ISO) is an acronym for tetrachlorodiphenylethane. Except in France, it is a generally



recognized name for the compound as a synthetic insecticide. This is true even though TDE is an alternative name for an unrelated compound, etoglucid, which is a chemically unrelated antineoplastic drug. For reasons that are obscure, the word DDD (an acronym for *dichlorodiphenyldichloroethane*) is used very much more commonly for 1,1-dichloro-2,2-bis(chlorophenyl)ethane when viewed as a metabolite of DDT or when used as a therapeutic drug, and this distinction has been retained in this book. As it happens, the term DDD also has two meanings; it is used for 2,2'-dihydroxy-6,6'-dinaphthyl disulfide as well as for the compound under discussion. Actually, almost everything we know about the compound relevant to humans is associated with its use as a drug rather than its use as an insecticide. Nonproprietary names for the *o,p'* isomer which is used as a drug include chlodithane (USSR) and mitotane (United States).

A proprietary name for the insecticide is Rhothane®. Code designations include D-3, ENT-4,225, ME-1,700, and NSC-38,721 (for *o,p'* isomer only).

**Physical and Chemical Properties** TDE has the empirical formula  $C_{14}H_{10}Cl_4$  and a molecular weight of 320.05. The pure material forms colorless crystals melting at 109–110°C. The technical material consists mainly of the *p,p'* isomer but also contains a substantial proportion of *o,p'* isomer and lesser proportions of related compounds. *p,p'*-TDE is more slowly dehydrochlorinated than *p,p'*-DDT, but TDE is incompatible with alkali. The solubilities are similar to those of DDT. The density of the technical material is 1.385.

**History, Formulations, Uses, and Production** The insecticidal properties of TDE were first described by Lauser *et al.* (1944). The formulations have included the technical material; wettable powders, 5%; emulsion concentrates, 25%; and dust, 5 and 10%.

### 15.3.2.2 Toxicity to Laboratory Animals

**Basic Findings** The effects of TDE are similar to those of DDT, but TDE is much less toxic in the rat and in humans. Gaines (1969) found the oral LD 50 in both male and female rats to be greater than 4000 mg/kg; Lehman (1951, 1952) reported 3400 mg/kg as an oral LD 50 in rats and 1200 as a dermal value in rabbits. Rabbits were killed quickly by dermal applications at the rate of 400 mg/kg/day; they were made severely ill but did not die when treated at the rate of 200 mg/kg/day for 90 days. In rats fed for 2 years, the lowest dietary level producing gross effects was 400 ppm and the lowest level fed (100 ppm, about 5 mg/kg/day) produced tissue damage. In the rat, pathology is indistinguishable from that caused by DDT (Lehman, 1951, 1952).

**Absorption, Distribution, Metabolism, and Excretion** The metabolism of *p,p'*-DDD has been described in Section 15.3.1.2.

Regardless of dosage form, 75% or more of *o,p'*-DDD is

absorbed from the gastrointestinal tract (Korpachev, 1972a). Following repeated doses, storage of *o,p'*-DDD reached its highest point in 10–20 days and then decreased somewhat in spite of continued intake. Elimination was rapid after treatment stopped but was detectable longest in the adrenals and adipose tissues (Korpachev, 1972b). The metabolism of *o,p'*-DDD in the rat has been investigated thoroughly by Reif and Sinsheimer (1975); their major results are summarized in Figure 15.3, which also records the metabolites found in humans by Reif *et al.* (1974). More recent studies to explain the covalent binding of *o,p'*-DDD in lung and adrenals are also described in Section 15.3.1.2.

**Biochemical Effects** The biochemical basis for the action of *o,p'*-DDD on the adrenal is not understood fully in connection with any species. It is clear that marked species differences exist. The mechanism that leads to prompt atrophy in the dog may be quite different from the mechanisms that limit the production or increase the breakdown of corticosteroids in species in which most or all of the adrenal cells stay alive.

It is clear that a reduction of steroid production accompanies atrophy of the adrenal of the dog. A review by Kupfer (1967) considered (a) reduced steroid production in species other than the dog, including the possibility that such reduction is secondary to inhibition of glucose-6-phosphate dehydrogenase activity in the adrenals, and (b) blockage of steroid action by a steroid metabolite formed under the influence of DDD. However, the existence of these effects, much less their importance, remains obscure. Hart and Straw (1971a) showed that administration of *o,p'*-DDD to dogs for only 2–48 hr completely blocked the normal increase in steroid production in response to ACTH *in vitro* but, paradoxically, produced a marked increase in the incorporation of labeled amino acids into protein of the slices. The same authors presented evidence that the site of action is the intramitochondrial conversion of cholesterol to pregnenolone (Hart and Straw, 1971b), specifically, ACTH-activated conversion and not baseline steroid production (Hart and Straw, 1971d). A secondary site involves inhibition of intramitochondrial conversion of 11-deoxycortisol to cortisol (Hart and Straw, 1971d). Further evidence supporting the importance of the primary site was offered by Komissarenko *et al.* (1972). *o,p'*-DDD inhibited ACTH-induced steroid production by more than 97% within 2 hr, and the active principle is either *o,p'*-DDD *per se* or a derivative formed in the adrenal gland of the intact dog (Hart and Straw, 1971c). *o,p'*-DDD applied to liver slices *in vitro* is not effective in reducing ACTH-induced steroidogenesis in the slices. However, the compound did reduce the formation of corticosteroid from progesterone or deoxycorticosterone added to homogenates made from adrenal cortices from dogs, chickens, rats, and human fetuses. These results are consistent with the view that the action of *o,p'*-DDD is to block 11- $\beta$ -hydroxylation (Kravchenko, 1973). Furthermore, a concentration of 16 ppm produced this effect in a monolayer culture of human fetal adrenal cells (Komissarenko *et al.*, 1971). Martz and Straw (1973) interpreted the decrease in adrenocortical heme and P-450 pro-



duced by *o,p'*-DDD in the dog as a suggestion that the compound is metabolized to a more active form, and this is supported by more recent *in vitro* studies with isolated adrenal mitochondria (Martz and Straw, 1980; Pohland and Counsell, 1985).

There is evidence for a peripheral action of *o,p'*-DDD on steroid transformation in humans also, although the site of action is different. This evidence was obtained by studying the excretion of metabolites of small injected doses of radioactive steroid both before and during administration of the drug. It was concluded that  $3\beta$ -hydroxy- $\Delta^5$ -steroid dehydrogenase was inhibited (Bradlow *et al.*, 1963).

Further evidence that *o,p'*-DDD has some inhibitory effect on the synthesis of corticosteroids in humans was provided by *in vitro* tests on adrenal tissue removed surgically from patients, some of whom had been under treatment with the drug. Total doses prior to surgery had varied from 324 to 2280 gm and had been given over periods of 1–12 months. Compounds whose synthesis (from radioactive precursors added to incubation flasks) was inhibited in tissue from treated patients were cortisol, corticosterone, 18-hydroxycorticosterone, and aldosterone (Touitou *et al.*, 1978). Direct addition of *o,p'*-DDD to human adrenal tissue *in vitro* was without effect on synthesis of corticosteroids.

Following massive dosage (60 mg/kg, iv), all of the isomers of DDD inhibit ACTH-induced steroid production in the dog, but the inhibition reached 50% of control in only 27 min after dosing with the *m,p'* isomer compared to 87 min with the *o,p'* isomer and 4–18 hr with the *p,p'* isomer. There was a marked temporal correlation between the percentage inhibition of ACTH-induced steroid production, the disruption of normal cellular structure of the innermost zones of the adrenal cortex, and the severity of the damage to mitochondria in these zones caused by the three isomers (Hart *et al.*, 1973). The effectiveness of *m,p'*-DDT for treating metastatic adrenocortical carcinoma had already been demonstrated (Nichols *et al.*, 1961).

However, in humans *m,p'*-DDD is less effective than *o,p'*-DDD (de Fossey *et al.*, 1968), and Reznikov (1973) found *m,p'*-DDD less effective in dogs also. Administration of *o,p'*-DDD to dogs is followed by a decrease in plasma albumin and an increase in globulins, especially  $\alpha_2$ -,  $\beta_1$ -, and  $\gamma$ -globulins (Van-yurykhina, 1972). The relation of these changes to the suppression of adrenal function is unknown, and their clinical significance is also unknown.

Guinea pigs receiving *o,p'*-DDD intraperitoneally at a rate of 100, 200, or 300 mg/kg/day for 20 days showed decreases in ascorbic acid levels corresponding to dosage (Petrin' and Nikulina, 1970). It was speculated that this might interfere with synthesis of corticosteroids.

Like other chlorinated hydrocarbon insecticides, *o,p'*-DDD stimulates hepatic microsomal oxygenation of both drugs and steroids and, according to a thorough review by Kupfer (1967), this may explain much of its action on corticoid metabolism in a wide range of species. Increased breakdown is evidenced by increased excretion of polar metabolites while nonpolar metabolites remain stable or even decrease—a finding encountered

in human patients (Hellman *et al.*, 1973). However, the demonstrated effect on corticoid metabolism fails to explain why *o,p'*- and *m,p'*-DDD are unique in their overall effects on the adrenal, including their ability to produce adrenocortical atrophy in the dog. Other powerful inducers of microsomal enzymes lack these effects. Furthermore, in some systems DDD is a relatively weak inducer compared, for example, to DDT and DDE (Gillett *et al.*, 1966). Whereas induction does occur in dogs, its interpretation is complex; for example, the induction caused by repeated doses can be suppressed by cortisol (Martz and Straw, 1972). Mikosha (1985) has proposed that inhibition of NADP reduction by malic enzyme in adrenals may play a role in *o,p'*-DDD action, perhaps by causing a decrease in steroid metabolism (Ojima *et al.*, 1985).

**Effects on Organs and Tissues** DDD is used to control different forms of adrenal overproduction of corticoids in humans (see Section 15.3.2.3). This therapy originally was based on the demonstration that DDD (Nelson and Woodard, 1948, 1949) and especially *o,p'*-DDD (Cueto and Brown, 1958; Komissarenko *et al.*, 1968) cause gross atrophy of the adrenals and degeneration of the cells of its inner cortex in dogs. This is true even though it was reported at the very first (Nelson and Woodard, 1948, 1949) that DDD produces almost no detectable damage to the adrenals of rats, mice, rabbits, and monkeys, and this finding was confirmed and extended by other investigators to other species, including humans (Zimmerman *et al.*, 1956; Komissarenko *et al.*, 1970). In the dog, *o,p'*-DDT produces gross atrophy of the adrenals when administered at a dosage of only 4 mg/kg/day. The dosage of technical grade DDD required to produce the same effect is 50–200 mg/kg/day (Cueto and Brown, 1958). However, in spite of its exceptional susceptibility, there is a definite threshold below which the dog does not respond. About 15% of technical DDT is *o,p'* isomer, much of which is gradually metabolized to *o,p'*-DDD. Yet dogs remained healthy and reproduced normally in a three-generation study involving dosages of technical DDT as high as 10 mg/kg/day (see Section 15.3.1.2).

DDD has been little used for Cushing's syndrome in dogs (Lubberink *et al.*, 1971), but it is effective at lower dosages than those used in humans, and side effects are less serious and less frequent (Schechter *et al.*, 1973).

It is an interesting fact that *p,p'*-DDE and the —OH analog of *p,p'*-DDD causes moderate hypertrophy of the dog adrenal and 2,2-bis(*p*-chlorophenyl)ethane causes moderate hyperplasia (Larson *et al.*, 1955).

The adrenal gland of the chicken, like that of the dog, undergoes some degeneration following treatment with *o,p'*-DDD (Komissarenko *et al.*, 1971).

The effect of DDD on thymolymphatic tissues is poorly understood. In one of the earliest studies of the compound, Lillie *et al.* (1947) reported that the spleen of all treated animals showed impressive siderosis. Much later Gawhary (1972) reported that, in rabbits, intramuscular injection of a commercial grade DDD (mainly *p,p'* isomer) caused acute atrophy of the thymus and hypertrophy of the adrenal, although the *m,p'*



isomer at a dosage of 100 mg/kg/day caused *hypertrophy* of the thymus and an increase in its choline acetylase activity. Decrease in the weight of the thymus and spleen as well as the adrenal glands of rats treated with *o,p'*-DDD was reported by Hamid *et al.* (1974).

Furthermore, Cueto and Moran (1968) and Cueto (1970) showed that, at a dosage of 50 mg/kg/day for 14 days, *o,p'*-DDD caused a gradually progressive hypotensive failure in dogs injected with epinephrine or norepinephrine, while leaving unchanged the cardioaccelerator and immediate pressor response of these drugs. The hypotensive failure was associated with weakening of the contractile force of the heart and with a reduction of plasma volume. The latter may have been caused by loss of fluid from the intravascular compartment and was not caused by release of histamine. The hypotensive state could be prevented to a significant degree by pretreatment with prednisolone.

The question of the hepatocarcinogenicity of chlorinated hydrocarbon insecticides is discussed in Section 15.2.3.2. In one test, no conclusion could be reached regarding either *p,p'*- or *o,p'*-DDD (Innes *et al.*, 1969). In another test in mice, *p,p'*-TDE at a dietary level of 250 ppm moderately increased the incidence of liver tumors in males only and increased the incidence of lung tumors in both sexes (Tomatis *et al.*, 1974a). The *o,p'* isomer was protective in rats treated earlier with the established carcinogen dimethylbenz[*a*]anthracene (DMBA) (Kravt'sova *et al.*, 1971). Leydig cell tumors were reported in the testis of rats receiving *o,p'*-DDD at the rate of 0.6 mg/kg/day for 285–348 days (Lacassagne, 1971). This report is inconsistent with other studies (Lehman, 1951, 1952), and this may indicate that a contaminant was involved. In an NCI study (1978a) there was a possible effect of TDE in causing an increased incidence of follicular cell carcinoma or follicular cell adenoma of the thyroid in male Osborne-Mendel rats but no effects in female B6C3F1 mice.

TDE was found not to be mutagenic in *Drosophila* (Vogel, 1972). It was found mutagenic in two of three indicator organisms in host-mediated tests but not in direct tests, suggesting that a metabolite was the active agent. However, in the same series of studies, both DDT and DDA were negative (Buselmaier *et al.*, 1973).

**Pathology** In addition to atrophy of the zona fasciculata and zona reticularis in the dog, *o,p'*-DDD changes the ultrastructure of most cell types of the anterior pituitary of that species. The most striking feature is an increase in corticotrophocytes such as is seen following adrenalectomy, and the increase in cells is presumably associated with increased production of ACTH. The hypothalamus also is involved (Gordienko and Kozyrskii, 1970; Gordienko *et al.*, 1973). In spite of their severe nature, the changes produced in the dog adrenal are at least partially reversible (Komissarenko *et al.*, 1972). Dosage-response relationships of mitochondrial swelling and of some other details of pathology in the dog adrenal have been explored by Gordienko and Kozyrskii (1973) and by Powers *et al.* (1974), who also investigated regeneration of the gland.

Hypertrophy of the thyroid in dogs receiving 25 mg/kg and its inhibition in those receiving 50 mg/kg had been reported (Gordienko *et al.*, 1972).

### 15.3.2.3 Toxicity to Humans

**Therapeutic Use** Following the demonstration that DDD caused atrophy of a part of the adrenal cortex of dogs, the compound has been used in humans in the hope of controlling excessive cortical secretion or of reducing the size of adrenal tumors. The underlying condition may be hyperplasia or adrenocortical carcinoma. Early attempts using mixed isomers and/or dosages less than 100 mg/kg/day often were ineffective, although side effects might be produced (Sheehan *et al.*, 1953). The dosage of *o,p'*-DDD has varied from 7 to 285 mg/kg/day, but a dosage of approximately 40 or more often 100 mg/kg/day for many weeks has been necessary to produce any benefit in humans (Bergental *et al.*, 1960; Gallagher *et al.*, 1962; Bledsoe *et al.*, 1964; Southern *et al.*, 1966a,b; Verdon *et al.*, 1962; Wallace *et al.*, 1961; Kommissarenko and Reznikov, 1970; Gutierrez and Crooke, 1980).

The effects of idiopathic hyperplasia may be controlled; in fact, a state of adrenal insufficiency may be produced (Canlorbe *et al.*, 1971; Sizonenko *et al.*, 1974).

*o,p'*-DDD also may give symptomatic relief of excessive production of androgens from a virilizing adrenal carcinoma Saez *et al.*, 1971; Helson *et al.*, 1971; Korth-Schutz *et al.*, 1977) or of adrenocortical activity secondary to a tumor that produces ACTH (Carey *et al.*, 1973).

Very early attempts to use DDD for treating Cushing's syndrome often failed because the *o,p'* isomer was not used and sometimes because the dosage was small. This was true of what apparently was the first therapeutic use (Sheehan *et al.*, 1953). Using the *o,p'* isomer, a favorable response is produced in about one-fourth to one-half of patients with inoperable adrenocortical carcinoma (Hutter and Kayhoe, 1966; Canlorbe *et al.*, 1971; Hoffman and Mattox, 1972; Lubitz *et al.*, 1973; Montgomery and Struck, 1973; Gutierrez and Crooke, 1980). In fact, an occasional cure, involving complete regression of metastases, is produced by chemotherapy including *o,p'*-DDD (Schick, 1973; Perevodchikova *et al.*, 1972; Harrison *et al.*, 1973; Pellerin *et al.*, 1975; Rappaport *et al.*, 1978). Other patients may live several years (Bricaire and Luton, 1977; McKierman *et al.*, 1978). More commonly, symptoms are relieved and life is prolonged only about 7–8 months or a little longer (Hutter and Kayhoe, 1966; Canlorbe *et al.*, 1971; Hoffman and Mattox, 1972; Lubitz *et al.*, 1973) or even less (Hajjar *et al.*, 1975). The success of treatment often is indicated early by a reduction of steroid excretion (Hoffman and Mattox, 1972; Lubitz *et al.*, 1973), but steroid excretion may increase, decrease, or remain unchanged (Fukushima *et al.*, 1971). Removal of the tumor and *o,p'*-DDD treatment may be combined (Levy *et al.*, 1985). The success of treatment is greater in Cushing's syndrome due to adrenal hyperplasia (Weisenfeld and Goldner, 1962). An early example of what appeared to be complete cure was reported by Bar-Hay *et al.*



(1964). Ten of 17 patients with this condition experienced cure or remission for 12–32 months after the drug had been withdrawn (Luton *et al.*, 1973).

The large dosage of *o,p'*-DDD necessary to produce clinical benefit often produces general lassitude, anorexia, nausea, vomiting, diarrhea, and/or dermatitis (Southern *et al.*, 1961; Weisenfeld and Goldner, 1962; Danowski *et al.*, 1964; Hutter and Kayhoe, 1966; Bochner *et al.*, 1969; Naruse *et al.*, 1970; Halmi and Lascari, 1971; Hoffman and Mattox, 1972; Nitschke and Link, 1972; Lubitz *et al.*, 1973; Perevodchikova *et al.*, 1972; Hajjar *et al.*, 1975; Gutierrez and Crooke, 1980). Apathy may range from mild dulling of interest to profound psychotic depression (Hoffman and Mattox, 1972). Gynecomastia, hematuria, leukopenia, and thrombocytopenia have been reported more rarely (Luton *et al.*, 1972; Perevodchikova *et al.*, 1972). The symptoms disappear soon after administration of the drug is stopped or the dosage is reduced. Furthermore, some patients do not develop toxicity. A 10-year-old girl received 7500 mg/day for a total of 9 kg without discernible side effects (Helson *et al.*, 1971).

Even large, therapeutic doses of *o,p'*-DDD cause no histological alterations of the adrenals in humans (Wallace *et al.*, 1961). However, electron microscopy revealed degenerative changes in the mitochondria of the zona fasciculata of a patient who had received *o,p'*-DDD at the rate of about 3000 mg/day for 1 month (Temple *et al.*, 1969). Dosages in the therapeutic range (specifically those between 110 and 140 mg/kg/day) produced no detectable injury to the liver, kidney, or bone marrow even though the patients exhibited the reversible symptoms listed earlier (Bergental *et al.*, 1960).

Kupfer (1967) reviewed the extensive literature indicating that the effect in humans and other species except the dog is caused by stimulation of corticoid metabolism by massive doses of *o,p'*-DDD and not to any direct effect on the adrenal. Southern *et al.* (1966a,b) agreed that the effect was predominantly extra-adrenal in humans when the drug was first given but offered evidence that adrenal secretion of cortisol eventually was reduced. Even though therapeutic doses eventually have a direct effect on the adrenal, doses encountered by workers exposed to technical DDT do not (Clifford and Weil, 1972; Morgan and Roan, 1973).

Somewhat encouraging results were reported in the use of *p,p'*-DDD for treating diabetics with hyaline vascular changes and hyperpolysaccharidemia (Törnblom, 1959). Apparently, there has been no attempt to use *o,p'*-DDD for this condition.

In addition to its rather extensive use for treating Cushing's syndrome, *o,p'*-DDD has been used in a much lower dosage for treating spanomenorrhea associated with hypertrichosis. Menstruation was restored in 13 of 15 women with these conditions, and normal pregnancies occurred in five of them during the treatment period. The babies were normal. There was some improvement in hypertrichosis in nine and no improvement in six (Klotz *et al.*, 1971).

At least part of the action of *o,p'*-DDT in controlling excessive androgens involves its action on their metabolism. It was found in a study of three patients with metastatic adrenal car-

cinoma and one with pernicious anemia that the compound decreased the conversion of labeled androgens to androsterone by about 76% and to etiocholanolone by about 80%. The main effect on androgen metabolism was consistent with induction of microsomal oxidase activity by the drug (Hellmann *et al.*, 1973).

When uptake of radioactive iodine is used for diagnosis of Cushing's syndrome, [<sup>131</sup>I]19-iodocholesterol is the compound usually employed. DDD labeled with <sup>131</sup>I has been used for the same purpose (Skromme-Kadlubik *et al.*, 1972, 1973a,b, 1974). No comparative study of the duration of storage of the two compounds appears to have been made. However, it is clear that it is possible to introduce enough radiation via <sup>131</sup>I-labeled DDD either to kill rodents or to cause atrophy of their adrenal glands, depending on the schedule of administration (Skromme-Kadlubik *et al.*, 1974). This has been viewed as an indication that <sup>131</sup>I-labeled DDD might be useful for treating human adrenal carcinoma. It certainly is an indication for caution in using the diagnostic technique in patients not already proved to have adrenal cancer.

**Laboratory Findings** Analytical study associated with what apparently was the first attempt to use *p,p'*-DDD in treating Cushing's syndrome established that the compound is concentrated in the adrenal gland. Eleven weeks after the last course of DDD, when the concentration in adipose tissue was less than half what it had been earlier, the concentration in an adrenal biopsy was 50 ppm, wet weight. On a lipid basis, the concentrations in fat and adrenal were almost identical (Sheehan *et al.*, 1953). A patient who had received *o,p'*-DDD at the rate of 4000 mg/day for 58 days had a blood level of 6 ppm and excreted 8.3 mg of free and 39.7 mg of conjugated DDA in a 24-hr urine sample (Sinsheimer *et al.*, 1972). There is evidence for two plasma pools of *o,p'*-DDD (Slooten *et al.*, 1982).

Normal volunteers excreted increased concentrations of DDA within 24 hr of receiving *p,p'*-DDD at a rate of 5 mg/day and continued to excrete DDA at greater than predose levels for over 4 months after dosing was stopped after 81 days (Roan *et al.*, 1971).

Treatment of appropriate cases with *o,p'*-DDT usually results in a decrease in urinary steroid excretion (Gutierrez and Crooke, 1980). An unusually detailed study of the individual compounds is that of Hartwig *et al.*, (1968).

In long-term administration of *o,p'*-DDD (2 gm/day for 1–3 months) to patients with adrenal carcinoma or Cushing's syndrome, Ojima *et al.* (1984) found that plasma levels of pregnenolone, progesterone, cortisol, corticosterone, and some other C<sub>21</sub> steroids were progressively decreased, as well as urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids. Touitou *et al.* (1985), however, have been unable to demonstrate any correlation between concentrations of *o,p'*-DDD in adrenals removed from patients preoperatively treated with the drug for Cushing's syndrome and inhibition of some steroid biosynthesis enzymes measured *in vitro*. There is a suggestion that *o,p'*-DDD suppresses ACTH-secreting cells in



[ 785 through 867 omitted ]



decone in the stool; the intestine itself seemed the most likely source (Boylan *et al.*, 1979). These observations also strongly suggest that reabsorption of chlordane from the intestine is largely dependent on the presence of bile.

The chlordecol found in human bile from poisoned workers was not present as the free alcohol to any great extent but mainly existed as the glucuronide (Fariss *et al.*, 1980). Another conjugate of chlordane was also detected, possibly formed by conjugation with glutathione. Unlike rat liver, human liver and gerbil liver (see Section 15.7.2.2) formed chlordecol by the action of an aldo-keto reductase (Molowa *et al.*, 1986a). The enzyme has been purified from human liver (Molowa *et al.*, 1986b). In fact, immunoblot analyses of seven human liver samples showed the presence in four of two immunoreactive proteins whose total concentration varied over a sixfold range. Interestingly, the half-time for the disappearance of chlordane from 22 exposed workers also varied as much as sixfold and was independent of the amount of chlordane initially detected in the blood (Cohn *et al.*, 1978). Of 28 chlordane-poisoned workers, only 8 patients had normal sperm counts and motility and only in one of these was chlordane greater than 1 ppm of blood (Cohn *et al.*, 1978; Guzelian, 1981, 1982b). Arrest of sperm maturation was also observed in testicular biopsies of two patients (Guzelian, 1982b).

**Pathology** Five sural nerve biopsies from workers affected by chlordane revealed an accumulation of elongated, electron-dense, crystalloid rods and short, laminated, and parallel-membranous bodies within Schwann cell cytoplasm; redundant Schwann cell cytoplasmic folds; prominent collagen pockets, focal degradation of axon cylinders containing condensed neurofilaments, neurotubules, and dense bodies; occasional demyelinated axons; and vacuolization of nonmyelinated fibers. The predominance of involvement of nonmyelinated and smaller myelinated fibers and relative sparing of the larger myelinated fibers may explain the clinical symptomatology and electromyographic findings (Martinez *et al.*, 1978).

Six skeletal muscle biopsies from the same group of workers revealed accumulations of lipofuscin and amorphous, electron-dense structures below the sarcolemma and between myofibrils of skeletal muscle (Martinez *et al.*, 1978).

Needle liver biopsies from chlordane-poisoned men showed minimal steatosis, focal proliferation of reticuloendothelial cells, and hypoglycogenation of nuclei. Livers were enlarged, and electron microscopic examinations showed residual bodies, branched mitochondria with paracrystalline inclusions, and proliferation of the endoplasmic reticulum (Guzelian *et al.*, 1980; Guzelian, 1985). Workers also had high levels of urinary glucuronic acid, which is proposed to be derived from the hepatic endoplasmic reticulum. In addition, workers displayed an enhanced clearance of antipyrine from the blood, which usually is taken as a sign of induction of the hepatic cytochrome P-450 drug-metabolizing system.

**Discussion** Whereas the acute toxicity of chlordane is only moderate, its high degree of cumulative effect in mice (Huber, 1965) is remarkable, and it was the subject of early publication.

In fact, the protracted nature of poisoning was known to the original manufacturer before production was first started (see Gleason *et al.*, 1963, reporting brief but critical information supplied by the manufacturer).

A point that deserves more emphasis than it has received is that chlordane is stored even more tenaciously by humans than by rodents. There was no way to predict this species difference, but routine analysis of serum samples would have detected the difference when little or no injury had occurred, and the results would have served as a warning to stop exposure. The lowest serum level eventually found associated with poisoning was one that would be alarming in connection with serum levels of other, more thoroughly studied chlorinated hydrocarbon insecticides. There seems little doubt that poisoning would have been avoided if proper attention had been given to the chemical and clinical aspects of occupational medicine and to the basic considerations of occupational hygiene.

It is interesting how much of the toxicity of chlordane in humans can be reproduced in experimental animals, and vice versa, especially if care is taken to pick the right model for a particular effect. This includes enlargement of the liver and induction of the drug-metabolizing system, an important point for toxicological and carcinogenic considerations. Unlike many poisoning episodes, the exposure of workers to chlordane has been used to investigate basic toxicological principles in humans with useful results such as the interindividual variability of a previously unknown aldo-keto reductase in liver (Molowa *et al.*, 1986b). Rational treatments for poisonings by these types of chemicals have also emerged (Guzelian, 1982a).

**Treatment of Poisoning** The only drug that has proved useful in poisoning by chlordane is cholestyramine. The use of this agent arose from careful consideration of data on the excretion of chlordane by humans and animals, followed by logical experiments in rats and humans (Boylan *et al.*, 1978; Cohn *et al.*, 1978; Guzelian, 1981, 1982a, 1984, 1985). Its effects may be due not only to direct binding of chlordane but to binding of bile salts which inhibit the nonbiliary intestinal excretion (Guzelian, 1982b). Because there is reason to think that cholestyramine might be useful for treating poisoning by some other chlorinated hydrocarbon insecticides also, it is described in Section 15.2.5.1. In spite of the importance of cholestyramine in the treatment of poisoning by chlordane, other matters relevant to treating poisoning by chlorinated hydrocarbon insecticides ought to be considered (see Section 15.2.5).

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## REFERENCES

- Abalis, I. M., Eldefrawi, M. E., and Eldefrawi, A. T. (1985). High-affinity stereospecific binding of cyclodiene and  $\gamma$ -hexachlorocyclohexane to  $\gamma$



- aminobutyric acid receptors of rat brain. *Pestic. Biochem. Physiol.* **24**, 95–102.
- Abalis, I. M., Eldefrawi, M. E., and Eldefrawi, A. T. (1986). Effect of insecticides on GABA-induced chloride influx into rat brain microsacs. *J. Toxicol. Environ. Health* **18**, 13–23.
- Abbott, D. C., Goulding, R., and Tatton, J. U'G. (1968). Organochlorine pesticide residues in human fat in Great Britain. *Br. Med. J.* **3**, 146–149.
- Abbott, D. C., Collins, G. B., and Goulding, R. (1972). Organochlorine pesticide residues in human fat in the United Kingdom 1969–71. *Br. Med. J.* **2**, 553–556.
- Abbott, D. C., Collins, G. B., Goulding, R., and Hoodless, R. A. (1981). Organochlorine pesticide residues in human fat in the United Kingdom 1976–1977. *Br. Med. J.* **283**, 1425–1428.
- Abbott, D. C., Goulding, R., Holmes, C. D., and Hoodless, R. A. (1985). Organochlorine pesticide residues in human fat in the United Kingdom 1982–1983. *Hum. Toxicol.* **4**, 435–445.
- Abdusaidov, T. (1972). Effects of thiamine, ascorbic acid, galascorbin, and cocarboxylase on the functional status of the liver in combined hexachlorane and dimethoate poisoning. *Med. Zh. Uzb.* **5**, 39–41 (in Russian).
- Abe, J., Inoue, Y., and Takamatsu, M. (1974). On the residual amounts of PCB and organochlorine pesticides in human blood. *Jpn. J. Hyg.* **29**, 93 (in Japanese).
- Abou-Donia, M. B., and Menzel, D. B. (1968). The metabolism *in vivo* of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) in the chick by embryonic injection and dietary ingestion. *Biochem. Pharmacol.* **17**, 2143–2146.
- Abraham, R., Benitz, K. F., and Mankes, R. (1983). Ploidy patterns in hepatic tumors induced by mirex. *Exp. Mol. Pathol.* **38**, 271–282.
- Abston, P. A., and Yarbrough, J. D. (1974). The *in vivo* effects of dietary mirex on hepatic lactic dehydrogenase and glutamic oxaloacetic transaminase levels of the rat. *J. Agric. Food Chem.* **22**, 66–68.
- Acker, L. (1974). Food chemistry for the benefit of consumer protection. *Dtsch. Lebensm.-Rundsh.* **70**, 5–12 (in German).
- Acker, L. (1981). Contamination of human milk with organochlorine pesticides. *Geburtshilfe Frauenheilkd.* **41**, 882–886 (in German).
- Acker, L., and Schulte, E. (1970). On the presence of chlorinated biphenyls and hexachlorobenzene in addition to chlorinated insecticides in human milk and human fat tissue. *Naturwissenschaften* **57**, 497 (in German).
- Acker, L., and Schulte, E. (1971). Organochlorine compounds in the human body. *Umschau* **61**, 32 (in German).
- Acker, L., and Schulte, E. (1972). Occurrence of hexachlorobenzene and polychlorinated biphenyls as well as chlorinated insecticides in human adipose tissue and milk. *Nahrung* **16**, 130 (in German).
- Acker, L., and Schulte, E. (1974). Organochlorine compounds in human fat. *Naturwissenschaften* **61**, 32 (in German).
- Ackerman, L. B. (1980). Overview of human exposure to dieldrin residues in the environment and current trends of residue levels in tissue. *Pestic. Monit. J.* **14**, 64–69.
- Adamovic, V. M., and Sokic, B. (1973). Lower level phenomena of DDT cumulation in female abdominal fatty tissue. *Arh. Hig. Rada Toksikol.* **24**, 303–306 (in Russian).
- Adamovic, V. M., Sokic, B., and Petrovic, O. (1971). On factors influencing the occurrence of organochlorine insecticides in newborns. *Ernaehrungsforschung* **16**, 579–585 (in German).
- Adamovic, V. M., Sokic, B., and Jonanovic-Similganski, M. (1978). Some observations concerning the ratio of the intake of organochlorine insecticides through food and amounts excreted in the milk of breast-feeding mothers. *Bull. Environ. Contam. Toxicol.* **20**, 280–285.
- Adams, M., Coon, F. B., and Poling, C. E. (1974). Insecticides in the tissues of four generations of rats fed different dietary fats containing a mixture of chlorinated hydrocarbon insecticides. *J. Agric. Food Chem.* **22**, 69–75.
- Adir, J., Caplan, Y. H., and Thompson, B. C. (1978). Kepone serum half-life in humans. *Life Sci.* **22**, 699–702.
- Agrawal, A. K., and Mehendale, H. H. (1984a). Perturbation of calcium homeostasis by  $\text{CCl}_4$  in rats pretreated with chlordecone and phenobarbital. *Environ. Health Perspect.* **57**, 289–291.
- Agrawal, A. K., and Mehendale, H. H. (1984b).  $\text{CCl}_4$ -induced alterations in  $\text{Ca}^{2+}$  homeostasis by chlordecone and phenobarbital pretreated animals. *Life Sci.* **34**, 141–148.
- Agrawal, A. K., and Mehendale, H. M. (1986). Effect of chlordecone on carbon tetrachloride-induced increase in calcium uptake in isolated perfused rat liver. *Toxicol. Appl. Pharmacol.* **83**, 342–348.
- Agrawal, A. K., Berndt, W. O., and Mehendale, H. M. (1983a). Possible nephrotoxic effect of carbon tetrabromide and its interaction with chlordecone. *Toxicol. Lett.* **17**, 57–62.
- Agrawal, A. K., Mohani, A., Zaid, N. F., and Seth, P. K. (1983b). Involvement of serotonergic receptors in endosulfan neurotoxicity. *Biochem. Pharmacol.* **32**, 3591–3593.
- Agrawal, D., Khanna, R. N., Anand, M., Gupta, G. S. D., and Ray, P. K. (1987). Lindane-induced changes in glucose and glutathione levels in cats. *Toxicol. Lett.* **38**, 77–82.
- Agthe, C., Garcia, H., Shubik, P., Tomatis, L., and Wenyon, E. (1970). Study of the potential carcinogenicity of DDT in the Syrian golden hamster. *Proc. Soc. Exp. Biol. Med.* **134**, 113–116.
- Agzamov, S. K. (1970). Conditions of the ear in persons involved in agricultural application of chemical poisons. *Med. Zh. Uzb.* **7**, 13–15 (in Russian).
- Ahmad, N., Harsas, W., Marolt, R. S., Morton, M., and Pollack, J. K. (1988). Total DDT and dieldrin content of human adipose tissue. *Bull. Environ. Contam. Toxicol.* **41**, 802–808.
- Ahmed, F. E., Hart, R. W., and Lewis, N. J. (1977). Pesticide induced damage and its repair in cultured human cells. *Mutat. Res.* **42**, 161–173.
- Ahmed, N. A., Rawi, J. M., and El-Behary, M. H. (1986). Effect of dieldrin injection on the level of certain amino acids and some enzymes in rat brain. *Comp. Biochem. Physiol. C* **85**, 437–442.
- Akasu, F. (1971). Maternity and pollution. *J. Jpn. Obstet. Gynaecol.* **23**, 759–764. (in Japanese).
- Alary, J. G., Guay, P., and Brodeur, J. (1971). Effect of phenobarbital on the metabolism of DDT in the rat and in the bovine. *Toxicol. Appl. Pharmacol.* **18**, 457–468.
- Albahary, C., Dubrisay, J., and Guérin, (1957). Refractory pancytopenia due to lindane (gamma BHC). *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **18**, 687–691 (in French).
- Albert, L. (1981). Organochlorine pesticide residues in maternal milk and their risk to health. *Bol. Of. Sanit. Panam.* **91**, 15–29.
- Albert, L., Cebrian, M. E., Mendez, F., and Portales, A. (1980). Organochlorine pesticide residues in human adipose tissue in Mexico: Results of a preliminary study in three Mexican cities. *Arch. Environ. Health* **35**, 262–269.
- Albert, L., Vega, P., and Portales, A. (1981). Organochlorine pesticide residues in human milk samples from Comarca Lagunera, Mexico, 1976. *Pestic. Monit. J.* **15**, 135–138.
- Albertson, T. E., Joy, R. M., and Stark, L. G. (1985). Facilitation of kindling in adult rats following neonatal exposure to lindane. *Dev. Brain Res.* **17**, 263–266.
- Albro, P. W., and Thomas, R. (1974). Intestinal absorption of hexachlorobenzene and hexachlorocyclohexane isomers in rats. *Bull. Environ. Contam. Toxicol.* **12**, 289–294.
- Aldegunde, M., Parafita, M., and Fernandez Otero, M. P. (1983). Effect of  $\gamma$ -hexachlorocyclohexane on serotonin metabolism in rat brain. *Gen. Pharmacol.* **14**, 303–305.
- Aldegunde Villar, M., Martin Fargueiro, I., Miguez Besada, I., and Fernandez Otero, M. P. (1981). Study of the mechanism of the hypothermic action of  $\gamma$ -hexachlorocyclohexane. *Acta Cient. Compostelana* **18**, 145–154.
- Aldous, C. N., Chetty, C. S., and Desai, D. (1983). Alterations in tissue distribution of chlordecone (Kepone) in the rat following phenobarbital or SKF-S25A administration. *J. Toxicol. Environ. Health* **11**, 365–372.
- Aldrich, F. D., and Holmes, J. H. (1969). Acute chlordane intoxication in a child. *Arch. Environ. Health* **19**, 129–132.
- Aldridge, W. N., Clothier, B., Forshaw, P., Johnson, M. K., Parker, V. H., Price, R. J., Skilleter, D. N., Verschoyle, R. D., and Stevens, C. (1978). The effect of DDT and the pyrethroids cismethrin and decamethrin on the acetyl choline and cyclic nucleotide content of rat brain. *Biochem. Pharmacol.* **27**, 1703–1706.
- Alekhina, S. M., and Khaykina, B. I. (1972). The effect of lindane on the



- activity of the lactate dehydrogenase and on its isoenzymatic spectrum. *Farmakol. Toksikol. (Moscow)* **35**, 734-737 (in Russian).
- Aleksandrowicz, D. R. (1979). Endosulfan poisoning and chronic brain syndrome. *Arch. Toxicol.* **43**, 65-68.
- Aleksieva, T., Vasilev, G., and Spasovski, M. (1959). Study of the toxic effects of DDT. *J. Hyg., Epidemiol., Microbiol. Immunol.* **5**, 8-15 (in Russian).
- Ali, S. F., Hong, J. S., Wilson, W. E., Lamb, J. C., Moore, J. A., Mason, G. A., and Bonely, S. C. (1982). Subchronic dietary exposure of rats to chlordane (Kepone) modifies levels of hypothalamic  $\beta$ -endorphin. *Neurotoxicology* **3**(2), 119-124.
- Alix, B., Courtadon, M., Jourde, M., Cassagnes, J., Chone, A. F., and Jallut, H. (1974). Acute benign pericarditis by pesticide inhalation—in relation to two cases. *Coeur Med. Interne* **13**, 165-169 (in French).
- Allen, A. L., Koller, L. D., and Pollock, G. A. (1983). Effect of toxaphene exposure on immune responses in mice. *J. Toxicol. Environ. Health* **11**, 61-69.
- Al-Omar, M. A., Tawfiq, S. J., and Al-Ogaily, N. (1985). Organochlorine residue levels in human milk from Baghdad. *Bull. Environ. Contam. Toxicol.* **35**, 65-67.
- Altmeier, G., Klein, W., and Korte, G. (1969). Contributions to ecological chemistry. XXIV. Metabolism of 14-C-endrin in perfused rat liver. *Tetrahedron Lett.* pp. 4269-4271.
- Alvarez, W. C., and Hyman, S. (1953). Absence of toxic manifestations in workers exposed to chlordane. *Arch. Ind. Hyg. Occup. Med.* **8**, 480-483.
- American Medical Association (AMA) (1952). American Medical Association Council on Pharmacy and Chemistry report on: Health hazards of electric vaporizing devices for insecticides. *JAMA, J. Am. Med. Assoc.* **149**, 367-369.
- American Medical Association (AMA) (1953). American Medical Association Council on Pharmacy and Chemistry report on: Health problems of vaporizing and fumigating devices for insecticides. *JAMA, J. Am. Med. Assoc.* **152**, 1232-1234.
- American Medical Association (AMA) (1954). American Medical Association Council on Pharmacy and Chemistry report on: Abuse of insecticide fumigating devices. *JAMA, J. Am. Med. Assoc.* **156**, 607.
- American Medical Association (AMA) (1960). American Medical Association Committee on Toxicology report on: Occupational dieldrin poisoning. *JAMA, J. Am. Med. Assoc.* **172**, 2077-2080.
- American Medical Association (AMA) (1986). "AMA Drug Evaluations," 3rd ed. Publishing Sciences Group, Littleton, Massachusetts.
- Ambrose, A. M., Christensen, H. Robbins, D., and Rather, L. (1953). Toxicology and pharmacological studies on chlordane. *Arch. Ind. Hyg. Occup. Med.* **7**, 197-210.
- Anagnostopoulos, M. L., Parlar, H., and Korte, F. (1974). Contribution to ecological chemistry LXXI: Isolation, identification and toxicology of some toxaphene components. *Chemosphere* **3**, 65-70 (in German).
- Anand, M., Khanna, R. N., Gopal, K., and Gupta, G. S. (1980). Effect of endosulfan on bioelectrical activity of brain in rats. *Vet. Hum. Toxicol.* **22**, 385-387.
- Anand, M., Akveld, A. C., and Saxena, P. R. (1981). Effect of a neurotoxic pesticide, endosulfan, on tissue blood flow in cats, including regional cerebral circulation. *Vet. Hum. Toxicol.* **23**, 252-258.
- Anand, M., Mehrotra, S., Gopal, K., Sur, R. N., and Chandra, S. V. (1985). Role of neurotransmitter in endosulfan induced aggressive behaviour in normal and lesioned rats. *Toxicol. Lett.* **24**, 79-84.
- Anand, M., Gopal, K., Agrawal, C., Chandra, S. V., Ray, P. K., Verma, M., and Shanker, K. (1986). Endosulfan induced inhibition of  $^3\text{H}$ -5-hydroxytryptamine uptake in platelets. *Toxicol. Lett.* **32**, 203-208.
- Andersen, J. R., and Orbaek, K. (1982). Organochlorine contaminants in human milk in Denmark, 1982. *Ambio* **13**, 266-268.
- Anderson, B. M., and Noble, C., Jr. (1977). *In vitro* inhibition of lactate dehydrogenase by Kepone. *J. Agric. Food Chem.* **25**, 28-31.
- Anderson, B. M., Noble, C., Jr., and Gregory, E. M. (1977). Kepone inhibition of malate dehydrogenases. *J. Agric. Food Chem.* **25**, 485-489.
- Anderson, T. W. (1985). DDT: Conclusion. *IARC Sci. Publ.* **65**, 119-121.
- Ando, M. (1982). Dose-dependent excretion of DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) in rats. *Arch. Toxicol.* **49**, 139-147.
- Angerer, J., Maass, R., and Heinrich, R. (1983). Occupational exposure to hexachlorocyclohexane. VI. Metabolism of  $\gamma$ -hexachlorocyclohexane in man. *Int. Arch. Occup. Environ. Health* **52**, 59-67.
- Angsubhakorn, S., Bhamarapravati, N., Pradesmnong, A., Im-Emgamol, N., and Sahaphong, S. (1989). Minimal dose and time protection by lindane ( $\gamma$ -isomer of 1,2,3,4,5,6-hexachlorocyclohexane) against liver tumors induced by aflatoxin B<sub>1</sub>. *Int. J. Cancer* **43**, 531-534.
- Anonymous (1958). Does BHC damage the bone marrow? *Br. Med. J.* **2**, 1522-1523.
- Anonymous (1972). BHC and DDT residues in human milk on the decline in Japan. *Nyaku Bijin* **56**, 458 (in Japanese).
- Anonymous (1975). Results of survey of pollution of human milk by polychlorobiphenyls and organochlorine pesticides. *Annu. Rep. Kyoto Munic. Inst. Public Health* **41**, 52-53 (in Japanese).
- Ansari, R. A., Siddiqui, M. K. J., and Gupta, P. K. (1984). Toxicity of endosulfan: Distribution of  $\alpha$ - and  $\beta$ -isomers of racemic endosulfan following oral administration in rats. *Toxicol. Lett.* **21**, 29-33.
- Apple, G., Morgan, D. P., and Roan, C. C. (1970). Determinants of serum DDT and DDE concentrations. *Bull. Environ. Contam. Toxicol.* **5**, 16-23.
- Aravinda Babu, K., Nigam, S. K., Lakkad, B. C., Bhatt, D. K., Karnik, A. B., Thakora, K. N., Kashyap, S. K., and Chatterjee, S. K. (1981). Effect of hexachlorocyclohexane on somatic and meiotic divisions in mole Swiss mice. *Bull. Environ. Contam. Toxicol.* **26**, 508-512.
- Arnold, D. W., Kennedy, G. L., Keplinger, M. L., and Calandra, J. C. (1977). Dominant lethal studies with technical chlordane, HCS-3260, and heptachlor: Heptachlor epoxide. *J. Toxicol. Environ. Health* **2**, 547-555.
- Arthur, R. D. (1976). "The Prevalence of and Types of Pesticides in the Air of the Mississippi Delta and the Blood Serum of the General Population of Mississippi," Final Report (E-32) from the Department of Biochemistry, Mississippi State University to the Epidemiological Studies Program, Technical Services Division, U.S. Environ. Prot. Agency, Washington, D.C.
- Artigas, F., Martinez, E., Canon, L., and Rodriguez-Farré, E. (1988a). Synthesis and utilization of neurotransmitters: Actions of subconvulsant doses of hexachlorocyclohexane isomers in brain monoamines. *Toxicology* **49**, 49-55.
- Artigas, F., Martinez, E., Canon, L., Gelpi, E., and Rodriguez-Farré, E. (1988b). Brain metabolites of lindane and related isomers: Identification by negative ion mass spectrometry. *Toxicology* **49**, 57-63.
- Artigas, F., Martinez, E., and Gelpi, E. (1988c). Organochlorine pesticides by negative ion chemical ionization. Brain metabolite of lindane. *Biomed. Mass. Spectrom.* **16**, 279-284.
- Askari, E. M., and Gabliks, J. (1973). DDT and immunological responses. II. Altered histamine levels and anaphylactic shock in guinea pigs. *Arch. Environ. Health* **26**, 309-312.
- Atallah, Y. H., and Dorough, H. Y. (1975). Insecticide residues in cigarette smoke, transfer and fate in rats. *J. Agric. Food Chem.* **23**, 64-71.
- Atrakchi, A. H., and West, T. C. (1985). Positive inotropy, calcium dependence and arrhythmogenicity of lindane in atrial tissue from the guinea pig. *Proc. West. Pharmacol. Soc.* **28**, 65-68.
- Attygalle, D. J., and Fernonda, W. D. L. (1959). Accidental poisoning with benzene hexachloride. *Ceylon Med. J.* **5**, 64-65.
- Atuma, S. S., and Vaz, R. (1986). A pilot study on levels of organochlorine compounds in human milk in Nigeria. *Int. J. Environ. Anal. Chem.* **26**, 187-192.
- Austin, H., Keil, J. E., and Cole, P. (1989). A prospective follow-up study of cancer mortality in relation to serum DDT. *Am. J. Public Health* **79**, 43-46.
- Avar, P., and Czeglédi-Janko, G. (1970). Occupational exposure to aldrin: Clinical and laboratory findings. *Br. J. Ind. Med.* **27**, 279-282.
- Avrahami, M., and Gemert, I. L. (1972). Hexachlorobenzene antagonism to dieldrin storage in adipose tissue. *N. Z. J. Agric. Res.* **15**, 783-787.
- Badayeva, L. N., and Kiseleva, N. I. (1976). Morphological changes in nervous structures in the body of mother and fetus during exposure to polychlorocamphene. *Vrach. Delo.* **2**, 109-113 (in Russian).
- Baggett, J. McC., Klein, R. L., Mehendale, H. M., and Thureson-Klein, A. K. (1977). Acute Kepone treatment of rats: A biochemical and ultrastructural study. *Pharmacologist* **19**, 199.
- Baggett, J. McC., Thureson-Klein, A., and Klein, R. L. (1980). Effects of chlordane on the adrenal medulla of the rat. *Toxicol. Appl. Pharmacol.* **52**, 313-322.
- Baker, M. T., and Van Dyke, R. A. (1984). Metabolism-dependent binding of the chlorinated insecticide DDT and its metabolite DDD to microsomal protein and lipid. *Biochem. Pharmacol.* **33**, 255-260.
- Baker, M. T., Nelson, R. M., and Van Dyke, R. A. (1985). The formation of chlorobenzene and benzene by the reductive metabolism of lindane in rat liver microsomes. *Arch. Biochem. Biophys.* **236**, 506-514.
- Baker, R. C., Coons, L. B., Mailman, R. B., and Hodgson, E. (1972). Induction of hepatic mixed function oxidases by the insecticide mirex. *Environ. Res.* **5**, 418-424.
- Bakshyev, N. S. (1973). Prophylaxis of pathology of the fetus and newborn child (experience of the Ukrainian SSR). *Vestn. Akad. Med. Nauk SSSR* **28**, 69-75 (in Russian).
- Bal, H. S. (1984). Effect of methoxychlor on reproductive systems of the rat. *Proc. Soc. Exp. Biol. Med.* **176**, 187-196.
- Balba, H. M., and Saha, J. G. (1978). Studies on the distribution, excretion, and metabolism of  $\alpha$ - and  $\gamma$ -isomers of  $^{14}\text{C}$  chlordane in rabbits. *J. Environ. Sci. Health, Part B* **13**, 211-233.
- Baldwin, M. K., and Robinson, J. (1969). Metabolism in the rat of the photoisomerization product of dieldrin. *Nature (London)* **224**, 283-284.
- Baldwin, M. K., Robinson, J., and Carrington, R. A. G. (1970a). Metabolism of HEOD (dieldrin) in the rat: Examination of the major fecal metabolite. *Chem. Ind. (London)*, pp. 595-597.
- Baldwin, M. K., Robinson, J., and Parke, D. V. (1970b). Metabolism of endrin in the rat. *J. Agric. Food Chem.* **18**, 1117-1123.
- Baldwin, M. K., Robinson, J., and Parke, D. V. (1972). A comparison of the metabolism of HEOD (dieldrin) in the CF1 mouse with that in the CFE rat. *Food Cosmet. Toxicol.* **10**, 333-351.
- Ball, W. W., Kay, K., and Sinclair, J. W. (1953). Observations on toxicity of aldrin. I. Growth and estrus in rats. *Arch. Ind. Hyg. Occup. Med.* **7**, 292-300.
- Baluja, G., Hernandez, L. M., Gonzalez, M. J., and Rico, M. C. (1982). Presence of organochlorine pesticides, polychlorinated biphenyls and mercury in Spanish milk samples. *Bull. Environ. Contam. Toxicol.* **28**, 573-577.
- Bamrov, C., Chomakov, M., and Dimitrova, N. (1966). Group intoxication with lindane. *Suvrem. Med.* **17**, 477-481 (in Russian).
- Bandyopadhyay, S. K., Tiwari, R. K., Bhattacharyya, A., and Chatterjee, G. C. (1982). Effect of dieldrin on rat liver plasma membrane enzymes. *Toxicol. Lett.* **11**, 131-134.
- Banerjee, B. D., and Hussain, Q. Z. (1986). Effect of sub-chronic endosulfan exposure on humoral and cell-mediated immune responses in albino rats. *Arch. Toxicol.* **59**, 279-284.
- Bann, J. M., DeCinco, T. J., Earle, N. W., and Sun, Y. P. (1956). The fate of aldrin and dieldrin in the animal body. *J. Agric. Food Chem.* **4**, 937-941.
- Bar-Hay, J., Benderly, A., and Rumney, G. (1964). Treatment of a case of nontumorous Cushing's syndrome with *o,p'*-DDD. *Pediatrics* **33**, 239-244.
- Barkve, H. (1961). Pesticides and a case of Dieldrex poisoning. *Tidsskr. Nor. Laegeforen.* **81**, 759-760 (in Norwegian).
- Barnes, J. M., and Heath, D. F. (1964). Some toxic effects of dieldrin in rats. *Br. J. Ind. Med.* **21**, 280-282.
- Barnes, R. (1967). Poisoning by the insecticide chlordane. *Med. J. Aust.* **1**, 972-973.
- Barnett, J. B., Soderberg, L. S. F., and Menna, J. H. (1985a). The effect of prenatal chlordane exposure on the delayed hypersensitivity response of BALB/c mice. *Toxicol. Lett.* **25**, 173-183.
- Barnett, J. B., Holcomb, D., Menna, J. H., and Soderberg, L. S. F. (1985b). The effect of prenatal chlordane exposure on specific anti-influenza cell-mediated immunity. *Toxicol. Lett.* **25**, 227-238.
- Barnett, R. W., D'Ercole, A. J., Cain, J. D., and Arthur, R. D. (1979). Organochlorine pesticide residues in human milk samples from women living in northwest and northeast Mississippi, 1973-1975. *Pestic. Monit. J.* **13**, 47-51.
- Baron, R. L., and Walton, M. S. (1971). Dynamics of HEOD (dieldrin) in adipose tissue of the rat. *Toxicol. Appl. Pharmacol.* **18**, 958-963.
- Barquero, M., and Constenla, M. A. (1986). Organochlorine pesticide residues in human adipose tissue in Costa Rica. *Rev. Biol. Trop.* **34**, 7-12 (in Spanish).
- Barquet, A., Morgade, C., and Pfaffenberger, C. D. (1981). Determination of organochlorine pesticides and metabolites in drinking water, human blood serum, and adipose tissue. *J. Toxicol. Environ. Health* **7**, 469-479.
- Bass, S. W., Triolo, A. J., and Coon, J. M. (1972). Effect of DDT on the toxicity and metabolism of parathion in mice. *Toxicol. Appl. Pharmacol.* **22**, 684-693.
- Batte, E. G., and Turk, R. D. (1948). Toxicity of some synthetic insecticides to dogs. *J. Econ. Entomol.* **41**, 102-103.
- Bauer, E., and Reisner, G. (1970). Panmyelophis after splashing with BHC in Austria. *Monatsschr. Ohrenheilkd. Laryngo-Rhinol.* **104**, 492-495 (in German).
- Baum, H., Black, R. F., and Kurtz, C. P. (1976). Dicofol: Collaborative study of the hydrolysable chlorine method. *J. Assoc. Off. Anal. Chem.* **59**, 1109-1112.
- Baumann, K., Angerer, J., Heinrich, R., and Lehnert, G. (1980). Occupational exposure to hexachlorocyclohexane. I. Body burdens of HCH-isomers. *Int. Arch. Occup. Environ. Health* **47**, 119-127.
- Baumann, K., Behling, K., Brassow, H.-L., and Stapel, K. (1981). Occupational exposure to hexachlorocyclohexane. III. Neurophysiological findings and neuromuscular function in chronically exposed workers. *Int. Arch. Occup. Environ. Health* **48**, 165-172.
- Bauza, C. F. (1975). Organochlorine pesticide residues in mothers' milk in Montevideo. *Arch. Pediatr. Urug.* **46**, 31-42.
- Bazulic, D., Stampar-Plasaj, B., Bujanovic, V., Stojanovski, N., Nastev, B., Rudelic, I., Sisul, N., and Zuzek, A. (1984). Organochlorine pesticide residues in the serum of mothers and their newborns from three Yugoslav towns. *Bull. Environ. Contam. Toxicol.* **32**, 265-268.
- Bedford, C. T., and Hutson, D. H. (1976). The comparative metabolism in rodents of the isomeric insecticides dieldrin and endrin. *Chem. Ind. (London)*, pp. 440-447.
- Bedford, C. T., Hutson, D. H., and Natoff, I. L. (1975a). The acute toxicity of endrin and its metabolites to rats. *Toxicol. Appl. Pharmacol.* **33**, 115-121.
- Bedford, C. T., Harrod, R. K., Hoadley, E. G., and Hutson, D. G. (1975b). The metabolic fate of endrin in the rabbit. *Xenobiotica* **5**, 485-500.
- Beemer, A. M., Kuttin, E. S., and Greenfield, S. (1970). An unusual case of dermatitis. *Harefuah* **78**, 112-113 (in Hebrew).
- Behrbohm, P., and Brandt, B. (1959). On allergic and toxic skin damage during preparation and processing of hexachlorocyclohexane. *Arch. Gewerbepathol. Gewerbehyg.* **17**, 365-383 (in German).
- Bell, A. (1960). Aldrin poisoning: A case report. *Med. J. Aust.* **2**, 698-700.
- Bell, A. N., Young, R. A., Lockard, V. G., and Mehendale, H. M. (1988). Protection of chlordane-potentiated carbon-tetrachloride hepatotoxicity and lethality by partial hepatectomy. *Arch. Toxicol.* **61**, 392-405.
- Bell, D., and MacLeod, A. F. (1983). Dieldrin pollution of a human food chain. *Hum. Toxicol.* **2**, 75-82.
- Bellward, G. D., Dawson, R., and Otten, M. (1975). The effect of dieldrin-contaminated feed on rat hepatic microsomal epoxide hydrazase and aryl hydrocarbon hydroxylase. *Res. Commun. Pathol. Pharmacol.* **12**, 669-684.
- Ben-Dyke, R., Sanderson, D. M., and Noakes, D. N. (1970). Acute toxicity data for pesticides. *World Rev. Pestic. Control* **9**, 119-127.
- Benet, H., Fujimori, K., and Ho, I. K. (1985). The basal ganglia in chlordane-induced neurotoxicity in the mouse. *Neurotoxicology* **6**(1), 151-158.
- Benezet, H. J., and Matsumura, F. (1973). Isomerization of  $\gamma$ -BHC to  $\alpha$ -BHC in the environment. *Nature (London)* **243**, 480-481.
- Berend, E., Kecskemeti, K., and Koppa, Gy. (1970). The level of chlorinated hydrocarbons in human tissues in Veszprem County. *Egeszsegudomány* **14**, 388-394 (in Hungarian).
- Bergental, D. M., Hertz, R., Lipsett, M. B., and Moy, R. H. (1960). Chemotherapy of adrenocortical cancer with *o,p'*-DDD. *Ann. Intern. Med.* **53**, 672-682.
- Bergman, K., Brandt, I., Appelgren, L. E., and Slamna, P. (1981). Structure-dependent, selective localization of chlorinated xenobiotics in the cerebellum and other brain structures. *Experientia* **37**, 1184-1185.



- Bernardelli, B. C., and Gennari, M. C. (1987). Death caused by ingestion of endosulfan. *J. Forensic Sci.* **32**, 1109-1112.
- Best, W. R. (1963). Drug-associated blood dyscrasias. *JAMA, J. Am. Med. Assoc.* **185**, 286-290.
- Bezuglyi, V. P., and Kaskevich, L. M. (1969). Some indices of the functional state of the liver in flying personnel engaged in aerial chemical operations. *Gig. Tr. Prof. Zabol.* **13**, 52-53 (in Russian).
- Bezuglyi, V. P., and Mukhtarova, N. D. (1969). The clinical aspects of acute polychloroprene poisoning. *Gig. Tr. Prof. Zabol.* **13**, 53-55 (in Russian).
- Bezuglyi, V. P., Odintsova, I. L., and Gorskaya, N. Z. (1973). Morphological composition of the blood in persons working with a complex of organo-chlorine and organophosphorus pesticides. *Vrach. Delo* **11**, 134-138.
- Bhaskaran, M., Sharma, R. C., and Bhide, N. K. (1979). DDT levels in human fat samples in Delhi area. *Indian J. Exp. Biol.* **17**, 1390-1392.
- Bhatia, S. C., and Venkatasubramanian, T. A. (1972). Mechanism of dieldrin-induced fat accumulation in rat liver. *J. Agric. Food Chem.* **20**, 993-996.
- Bhatt, D. K., Nigam, S. K., Aravinda-Babu, K., Lakkad, B. C., Kamik, A. B., Thakore, K. N., Kashyap, S. K., and Chatterjee, S. K. (1981). Histochemical changes in ATPase distribution during hexachlorocyclohexane induced hepatocarcinogenesis in inbred Swiss mice. *Indian J. Exp. Biol.* **19**, 621-624.
- Bick, M. (1967). Chlorinated hydrocarbon residues in human body fat. *Med. J. Aust.* **1**, 127-129.
- Bickel, M. H. (1984). The role of adipose tissue in the distribution and storage of drugs. *Prog. Drug Res.* **28**, 273-303.
- Bidwell, K., Weber, E., Nienhold, I., Connor, T., and Legator, M. S. (1975). Comprehensive evaluation for mutagenic activity of dieldrin. *Mutat. Res.* **31**, 314.
- Biros, F. J., and Enos, H. F. (1973). Oxychlordane residues in human adipose tissues. *Bull. Environ. Contam. Toxicol.* **10**, 257-260.
- Bishara, R. H., Born, G. S., and Christian, J. E. (1972). Radiotracer distribution and excretion study of chlorophenothane in rats. *J. Pharm. Sci.* **61**, 1912-1916.
- Biskind, M. S. (1952). The new insecticides and the public health. *Harefuah* **44**, 9-13 (in Hebrew).
- Biskind, M. S. (1953). Public health aspects of the new insecticides. *Am. J. Dig. Dis.* **20**, 331-341.
- Biskind, M. S., and Bieber, I. (1949). DDT poisoning—a new syndrome with neuro-psychiatric manifestations. *Am. J. Psychother.* **3**, 261-270.
- Bjerk, J. E. (1972). DDT and polychlorinated biphenyl residues in human material in Norway. *Tidsskr. Nor. Laegeforen.* **92**, 15-19 (in Norwegian).
- Black, A. M. S. (1974). Self poisoning with dieldrin: A case report and pharmacokinetic discussion. *Anaesthesiol. Intens. Care* **2**, 369-374.
- Blanke, R. V., Fariss, M. W., Guzelian, P. S., Patterson, A. R., and Smith, D. E. (1978). Identification of a reduced form of chlordane (Kepone) in human stool. *Bull. Environ. Contam. Toxicol.* **20**, 782-785.
- Blazquez, J., and Bianchini, C. (1956). Chronic occupational intoxication by dieldrin in man. *Gac. Med. Caracas* **63**, 1-39 (in Spanish).
- Blazquez, J., and Bianchini, C. (1957). Study of the first cases of intoxication by dieldrin and application of xenobiosis in people. *Bol. Of. Sanit. Panam.* **43**, 504-511 (in Spanish).
- Bledsoe, T., Roland, D. P., Hey, R. L., and Liddle, G. W. (1964). An effect of *o,p'*-DDD on extra-adrenal metabolism of cortisol in man. *J. Clin. Endocrinol. Metab.* **24**, 1303-1311.
- Bleiberg, M. J., and Larson, P. S. (1957). Studies on the adrenocortical effects and metabolism of 2,2 bis-(*p*-ethylphenyl)-1,1-dichloroethane (Perthane). *J. Pharmacol. Exp. Ther.* **119**, 133-134.
- Blekherman, N. A., and Il'yina, V. I. (1972). Some ovarian and adrenal cortex hormonal function indexes in women working with organochlorine pesticides. *Fiziol. Zh (Kiev, 1955-1977)* **18**, 268-270 (in Ukrainian).
- Blend, M. J., and Lehnert, B. E. (1973). Luteinizing hormone serum levels and body weight/organ weight ratios in male rats fed low levels of dieldrin. *Ind. Med.* **42**, 18.
- Blisard, K. S., Kornfeld, M., McFeeley, P., and Smialek, J. E. (1986). The investigation of alleged insecticide toxicity: A case involving chlordane exposure, multiple sclerosis and peripheral neuropathy. *J. Forensic Sci.* **31**, 1499-1504.
- Bloomer, A. W., Nash, S. I., Price, H. A., and Welch, R. L. (1977). A study of pesticide residues in Michigan's general population. *Pestic. Monit. J.* **11**, 111-115.
- Bloomquist, J. R., and Soderlund, D. M. (1985). Neurotoxic insecticides inhibit GABA-dependent chloride uptake by mouse brain vesicles. *Biochem. Biophys. Res. Commun.* **133**, 37-43.
- Bloomquist, J. R., Adams, P. M., and Soderlund, D. M. (1986). Inhibition of  $\gamma$ -aminobutyric acid stimulated chloride flux in mouse brain vesicles by polychlorocycloalkane and pyrethroid insecticides. *Neurotoxicology* **7**(3), 11-120.
- Bochkovskii, F. R., and Riabov, V. G. (1970). Polychloroprene poisoning. *Sud.-Med. Ekspert.* **13**, 48-49 (in Russian).
- Bochner, F., Lloyd, H. M., Roeser, H. P., and Thomas, M. J. (1969). Effects of *o,p'*-DDD and aminoglutethimide on metastatic adrenocortical carcinoma. *Med. J. Aust.* **1**, 809-812.
- Bogusz, M. (1968). Influence of insecticides on the activity of some enzymes contained in human serum. *Clin. Chim. Acta* **19**, 367-369.
- Boiko, V. G., and Krasnyuk, E. P. (1969). Clinical characteristics of the pathology of respiratory tracts of persons working with DDT. *Zh. Ushn., Nos. Gorl. Bolezn.* **29**, 35-38 (in Russian).
- Bojanowska, A., Jonczyk, H., Rudowski, W., Traczyk, Z., and Klawe, Z. (1973). DDT and  $\alpha$ -BHC content in blood and fatty tissue of subjects not professionally exposed to these compounds. *Pol. Tyg. Lek.* **28**(51), 1999-2001 (in Polish).
- Bonderman, D. P., Mick, D. L., and Long, K. R. (1971). Occupational exposure to aldrin, 2,4-D and 2,4,5-T and its relationship to sterases. *Ind. Med. Surg.* **40**, 23-27.
- Bondy, S. C., and Halsall, L. (1988). Lindane-induced modulation of calcium levels with synaptosomes. *Neurotoxicology* **9**, 645-652.
- Boucard, M., Beaulaton, I. S., Mestres, R., and Allieu, M. (1970). Experimental study of teratogenesis: Influence of the period and duration of treatment. *Therapie* **25**, 907-913 (in French).
- Bowerman, J. G., Gomez, M. P., Austin, R. D., and Wold, D. E. (1987). Comparative study of permethrin 1% creme rinse and lindane shampoo for the treatment of head lice. *Pediatr. Infect. Dis. J.* **6**, 252-255.
- Boyd, E. M., and Chen, C. P. (1968). Lindane toxicity and protein-deficient diet. *Arch. Environ. Health* **17**, 156-163.
- Boyd, E. M., and Dobos, I. (1969). Protein deficiency and tolerated oral doses of endosulfan. *Arch. Int. Pharmacodyn. Ther.* **178**, 152-165.
- Boyd, E. M., and Stefec, J. (1969). Dietary protein and pesticide toxicity, with particular reference to endrin. *Can. Med. Assoc. J.* **101**, 335-339.
- Boyd, E. M., and Taylor, F. I. (1971). Toxaphene toxicity in protein-deficient rats. *Toxicol. Appl. Pharmacol.* **18**, 158-167.
- Boyd, E. M., Chen, C. P., and Krijen, C. J. (1969). Lindane and dietary protein. *Pharmacol. Res. Commun.* **1**, 403-412.
- Boyd, E. M., Dobos, I., and Krijnen, C. J. (1970). Endosulfan toxicity and dietary protein. *Arch. Environ. Health* **21**, 15-19.
- Boylan, J. J., Egle, J. L., and Guzelian, P. S. (1978). Cholestyramine: Use as a new therapeutic approach for chlordane (Kepone) poisoning. *Science* **199**, 893-895.
- Boylan, J. J., Cohn, W. J., Egle, J. L., Blanke, R. V., and Guzelian, P. S. (1979). Excretion of chlordane by the gastrointestinal tract: Evidence for a nonbiliary mechanism. *Clin. Pharmacol. Ther.* **25**, 579-585.
- Brade, W. P., Chiu, J. F., and Hnilica, L. S. (1974). Phosphorylation of rat liver nuclear acidic phosphoproteins after administration of  $\alpha$ -1,2,3,4,5,6-hexachlorocyclohexane *in vivo*. *Mol. Pharmacol.* **10**, 398-405.
- Bradlow, H. L., Fukushima, D. K., Zumoff, B., Hellman, L., and Gallagher, T. F. (1963). A peripheral action of *o,p'*-DDD on steroid biotransformation. *J. Clin. Endocrinol. Metab.* **23**, 918-922.
- Bradt, P. T., and Herrenkohl, R. C. (1976). DDT in human milk: What determines the levels? *Sci. Total Environ.* **6**, 161-163.
- Brady, M. N., and Siyali, D. S. (1972). Hexachlorobenzene in human fat. *Med. J. Aust.* **1**, 158-161.
- Brandt, I., and Hogman, P. (1980). Selective binding of aldrin and dieldrin in cartilage. *Arch. Toxicol.* **45**, 223-226.
- Brassow, H.-L., Baumann, K., and Lehnert, G. (1981). Occupational exposure to hexachlorocyclohexane. II. Health conditions of chronically exposed workers. *Int. Arch. Occup. Environ. Health* **48**, 81-87.
- Bratowski, T. A., and Matsumura, F. (1972). Properties of a brain adenosine triphosphatase sensitive to DDT. *J. Econ. Entomol.* **65**, 1238-1245.
- Braund, D. G., Langlois, B. E., Conner, D. J., and Moore, E. E. (1971). Feeding phenobarbital and activated carbon to accelerate dieldrin residue removal in a contaminated herd. *J. Dairy Sci.* **54**, 435-438.
- Brevik, E. M., and Bjerk, J. E. (1978). Organochlorine compounds in Norwegian human fat and milk. *Acta Pharmacol. Toxicol.* **43**, 59-63.
- Brewton, H. V., and McGrath, H. J. W. (1967). Insecticides in human fat in New Zealand. *N. Z. J. Sci.* **10**, 486-492.
- Bricaire, H., and Luton, J. P. (1977). Does *o',p*-DDD possess antimutagenic action? Reflections on its use in the treatment of suprarenal adenocarcinomas. *Nouv. Presse Med.* **6**, 3650 (in French).
- Brimfield, A. A., and Street, J. C. (1979). Mammalian biotransformation of chlordane: *In vivo* and primary hepatic comparisons. *Ann. N. Y. Acad. Sci.* **320**, 247-256.
- Brimfield, A. A., and Street, J. C. (1981). Microsomal activation of chlordane isomers to derivatives that irreversibly interact with cellular macromolecules. *J. Toxicol. Environ. Health* **7**, 193-206.
- Brittebo, E. G., Hogman, P. G., and Brandt, I. (1987). Epithelial binding of hexachlorocyclohexanes in the respiratory and upper alimentary tracts: A comparison between  $\alpha$ -,  $\beta$ -, and  $\gamma$ -isomers in mice. *Food Chem. Toxicol.* **25**, 773-780.
- Bronisz, H., and Ochynski, J. (1968). DDT and DDE in human milk (in Polish).
- Bronisz, H., Rusiecki, W., Ochynski, J., and Bernhard, E. (1967). DDT in adipose tissue of Polish population. *Diss. Pharm. Pharmacol.* **19**, 309-314.
- Brooks, G. T. (1973). The design of insecticidal chlorohydrocarbon derivatives. In "Drug Design" (E. J. Ariens, ed.), Vol. 4. Academic Press, New York.
- Brooks, G. T., and Harrison, A. (1969). Hydration of HEOD (dieldrin) and heptachlor epoxides by microsomes from the livers of pigs and rabbits. *Bull. Environ. Contam. Toxicol.* **4**, 352-361.
- Brooks, G. T., Harrison, A., and Lewis, S. E. (1970). Cyclodiene epoxide ring hydration by microsomes from mammalian liver and houseflies. *Biochem. Pharmacol.* **19**, 255-273.
- Brown, J. R. (1967). Organo-chlorine pesticides residues in human depot fat. *Can. Med. Assoc. J.* **97**, 367-373.
- Brown, J. R. (1972). The effect of dietary kelthane on mouse and rat reproduction. *Pestic. Chem., Proc. Int. IUPAC Congr. Pestic. Chem.*, 2nd, 1971, Vol. 6, pp. 531-548.
- Brown, J. R., and Chow, L. Y. (1975). Comparative study of DDT and its derivatives in human blood samples in Norfolk County and Holland Marsh, Ontario. *Bull. Environ. Contam. Toxicol.* **13**(4), 483-488.
- Brown, J. R., Hughes, H., and Viriyanondha, S. (1969). Storage, distribution and metabolism of 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol. *Toxicol. Appl. Pharmacol.* **15**, 30-37.
- Brown, L. D., Wilson, D. E., and Yarbrough, J. D. (1988). Alterations in the hepatic glycoconjugate response to mirex treatment. *Toxicol. Appl. Pharmacol.* **92**, 203-213.
- Brown, M. A., and Casida, J. E. (1987). Metabolism of a dicofol impurity  $\alpha$ -chloro-DDT, but not dicofol or dechlorodicofof, to DDE in mice and a liver microsomal system. *Xenobiotica* **17**, 1169-1174.
- Brown, V. K. H., Chambers, P. L., Hunter, C. G., and Stevenson, D. E. (1962). "The Toxicity of Telodrin for Vertebrates," Tunstall Lab. Rep. R(T)-2-62 (cited by Jager, 1970).
- Brown, V. K. H., Hunter, C. G., and Richardson, A. (1964). A blood test diagnostic of exposure to aldrin and dieldrin. *Br. J. Ind. Med.* **21**, 283-286.
- Brown, V. K. H., Robinson, J., and Thorpe, E. (1974). The toxicity of dieldrin (HEOD) to domestic fowl. *Pestic. Sci.* **5**, 567-586.
- Bruevich, T. S. (1964). Occupational dermatoses of disinfectant operators provoked by hexachlorane. *Gig. Tr. Prof. Zabol.* **8**, 28-32.
- Buck, A. A., and Pfannenmueller, L. (1957). Intoxications with hexachlorocyclohexane. *Arch. Toxicol.* **16**, 328-335.
- Bulger, W. H., and Kupfer, D. (1977). The *in vivo* and *in vitro* estrogenic activity of methoxychlor and its bis-phenolic analog 2,2bis(BPHT) in the rat. *Pharmacologist* **19**, 199.
- Bulger, W. H., Muccitelli, R. M., and Kupfer, D. (1978a). Studies on the *in vivo* and *in vitro* estrogenic activities of methoxychlor and its metabolites. Role of hepatic mono-oxygenase in methoxychlor activation. *Biochem. Pharmacol.* **27**, 2417-2423.
- Bulger, W. H., Muccitelli, R. M., and Kupfer, D. (1978b). Interactions of methoxychlor, methoxychlor base-soluble contaminant, and 2,2-bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane with rat uterine estrogen receptor. *J. Toxicol. Environ. Health* **4**, 881-893.
- Bulger, W. H., Muccitelli, R. M., and Kupfer, D. (1979). Studies on the estrogenic activity of chlordane (Kepone) in the rat: Effects on uterine receptor. *Mol. Pharmacol.* **15**, 515-524.
- Bulger, W. H., Temple, J. E., and Kupfer, D. (1983). Covalent binding of [ $^{14}$ C]methoxychlor metabolite(s) to rat liver microsomal components. *Toxicol. Appl. Pharmacol.* **63**, 367-374.
- Bulger, W. H., Feil, V., and Kupfer, D. (1985). Role of hepatic monooxygenases in generating estrogenic metabolites from methoxychlor and from identified contaminants. *Mol. Pharmacol.* **27**, 115-124.
- Bunch, T. D., and Low, J. B. (1973). Effects of dieldrin on chromosomes of semi-domestic mallard ducks. *J. Wildl. Manage.* **37**, 51-57.
- Bungay, P. M., Dedrick, R. C., and Mathews, H. B. (1981). Enteric transport of chlordane (Kepone) in the rat. *J. Pharmacokin. Biopharm.* **9**, 309-341.
- Bunyan, P. J., Townshend, M. G., and Taylor, A. (1972). Pesticide induced changes in hepatic microsomal enzyme systems: Some effects of 1,1-di(*p*-chlorophenyl)-2,2,2-trichloroethane (DDT) and 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene (DDE) in the rat and Japanese quail. *Chem.-Biol. Interact.* **5**, 13-26.
- Burchfield, J. L., Duffy, F. H., and Sim, V. M. (1976). Persistent effects of sarin and dieldrin upon the primate electroencephalogram. *Toxicol. Appl. Pharmacol.* **35**, 365-379.
- Burkatzkaya, E. N. (1963). The effect of hexachlorocyclohexane  $\gamma$ -isomer on the immunobiological reactivity of the body. *Gig. Sanit.* **28**, 29-33 (in Russian).
- Burkatzkaya, E. N., Ivanova, E. V., and Krasniuk, E. P. (1959). Working hygiene and the state of health of workers producing insecticides containing BHC. *Gig. Sanit.* **24**, 17-22 (in Russian).
- Burkatzkaya, E. N., Voitenko, G. A., and Krasniuk, E. P. (1961). Working conditions and health status of workers at DDT production plants. *Gig. Sanit.* **26**, 24-29 (in Russian).
- Burlington, H., and Linderman, V. F. (1950). Effect of DDT on testes and secondary sex characteristics of White Leghorn cockerels. *Proc. Soc. Exp. Biol. Med.* **74**, 48-51.
- Burns, E. C., Dahm, P. A., and Lindquist, D. A. (1957). Secretion of DDT metabolites in the bile of rats. *J. Pharmacol. Exp. Ther.* **121**, 55-62.
- Burns, J. E. (1974). Organochlorine pesticide and polychlorinated biphenyl residues in biopsied human adipose tissue—Texas 1969-72. *Pestic. Monit. J.* **7**, 122-126.
- Bursch, W., and Schulte-Hermann, R. (1983). Synchronization of hepatic DNA synthesis by scheduled feeding and lighting in mice treated with the chemical inducer of liver growth  $\alpha$ -hexachlorocyclohexane. *Cell Tissue Kinet.* **16**, 125-134.
- Buselmaier, W., Röhrborn, G., and Propping, P. (1973). Comparative investigations on the mutagenicity of pesticides in mammalian test systems. *Mutat. Res.* **21**, 25-26.
- Byard, J. L., and Pittman, K. A. (1975). Early liver changes produced by mirex and their reversibility. *Toxicol. Appl. Pharmacol.* **33**, 130.
- Byard, J. L., Koepke, U. C., Abraham, R., Goldberg, L., and Coulston, F. (1974). Biochemical changes produced in the liver by mirex. *Toxicol. Appl. Pharmacol.* **29**, 126-127.
- Byard, J. L., Koepke, U. C., Abraham, R., Goldberg, L., and Coulston, F. (1975). Biochemical changes in the liver of mice fed mirex. *Toxicol. Appl. Pharmacol.* **33**, 70-77.
- Byrd, R. A., Young, J. F., Kimmel, C. A., Morris, M. D., and Holson, J. F. (1982). Computer simulation of mirex pharmacokinetics in the rat. *Toxicol. Appl. Pharmacol.* **66**, 182-192.
- Cabral, J. R. P. (1985). DDT: Laboratory evidence. *IARC Sci. Publ.* **65**, 101-105.



- Cabral, J. R. P., Testa, M. C., and Terracini, B. (1972). Lack of long-term effects from heptachlor administration to suckling rats. *Tumori* **58**, 49–53.
- Cabral, J. R. P., Raitano, F., Mollner, T., Bronczyk, S., and Shubik, P. (1979a). Acute toxicity of pesticides in hamsters. *Toxicol. Appl. Pharmacol.* **48**, A192.
- Cabral, J. R. P., Hall, R. K., Bronczyk, S. A., and Shubik, P. (1979b). A carcinogenicity study of the pesticide dieldrin in hamsters. *Cancer Lett.* **6**, 241–246.
- Cabral, J. R. P., Hall, R. K., Rossi, L., Bronczyk, S. A., and Shubik, P. (1982a). Lack of carcinogenicity of DDT in hamsters. *Tumori* **68**, 5–10.
- Cabral, J. R. P., Hall, R. K., Rossi, L., Bronczyk, S. A., and Shubik, P. (1982b). Effects of long-term intake of DDT in rats. *Tumori* **68**, 11–17.
- Cameron, G. R. (1945). Risks to man and animals from the use of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT): With a note on the toxicity of chlorophenyl-1,1,1-trichloroethane (DDT). *Br. Med. Bull.* **3**, 233–235.
- Cameron, G. R., and Burgess, F. (1945). The toxicity of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT). *Br. Med. J.* **1**, 865–871.
- Camon, L., Sola, C., Martinez, E., Sanfeliu, C., and Rodriguez-Farré, E. (1988a). Cerebral glucose uptake in lindane-treated rats. *Toxicology*, **49**, 381–387.
- Camon, L., Martinez, E., Artigas, F., Sola, C., and Rodriguez-Farré, E. (1988b). The effect of nonconvulsant doses of lindane on temperature and body weight. *Toxicology*, **49**, 389–394.
- Campos, H. A., and Jurue, H. (1970a). A histamine-dependent increase of 5-hydroxytryptamine in the rat brain *in vivo*. *Experientia*, **26**, 613–614.
- Canada (1962). "Chlordane Poisoning. Information Release to Poison Control Centers." Release No. 2. Reprinted in: "World Health Organization Information Circular on Toxicity of Pesticides to Man," No. 11, p. 10. World Health Organ., Geneva, 1963.
- Canlorbe, P., Bader, J. C., and Job, J. C. (1971). Diagnostic problems arising from a virilizing tumor of the adrenal cortex. (Case report—literature review.) *Sem. Hop.* **47**, 2255–2270 (in French).
- Cannon, A. B., and McRae, M. R. (1948). Treatment of scabies. *JAMA, J. Am. Med. Assoc.* **138**, 557–560.
- Cannon, S. B., and Kimbrough, R. D. (1979). Short-term chlordecone toxicity in rat including effects on reproduction, pathological organ changes and their reversibility. *Toxicol. Appl. Pharmacol.* **47**, 469–476.
- Cannon, S. B., Veazey, J. M., Jackson, R. S., Burse, V. W., Hayes, C., Straub, W. E., Landrigan, P. J., and Liddle, J. A. (1978). Epidemic Kepone poisoning in chemical workers. *Am. J. Epidemiol.* **107**, 529–537.
- Carey, R. M., Orth, D. N., and Hartmann, W. H. (1973). Malignant melanoma with ectopic production of adrenocorticotrophic hormone: Palliative treatment with inhibitors of adrenal steroid biosynthesis. *J. Clin. Endocrinol. Metab.* **36**, 482–487.
- Carlson, D. A., Konyha, K. D., Wheeler, W. B., Marshall, G. P., and Zaylshe, R. G. (1976). Mirex in the environment: Its degradation to Kepone and related compounds. *Science* **194**, 939–941.
- Carlson, J., and Abraham, R. (1985). Nuclear ploidy of neonatal rat livers: Effects of two hepatic carcinogens (mirex and diethylnitrosamine). *J. Toxicol. Environ. Health* **15**, 551–559.
- Carlson, J. N., and Rosellini, R. A. (1987). Exposure to low doses of the environmental chemical dieldrin causes behavioural deficit in animals prevented from coping with stress. *Psychopharmacology* **91**, 122–126.
- Carlson, L. A., and Kolomod-Hedman, B. (1977). Decrease in  $\alpha$ -lipoprotein cholesterol in men after cessation of exposure to chlorinate hydrocarbon pesticides. *Acta Med. Scand.* **201**, 375–376.
- Carmine, E. L., Carchman, R. A., and Borzelleca, J. F. (1979). Kepone: Cellular sites of action. *Toxicol. Appl. Pharmacol.* **49**, 543–550.
- Carrero, I., Fernandez-Moreno, M. D., Pérez-Albarsanz, M. A., and Prieto, J. C. (1989). Lindane effect upon the vasoactive intestinal peptide receptor/effecter system in rat enterocytes. *Biochem. Biophys. Res. Commun.* **159**, 1391–1396.
- Carrillo, S. J. (1954). The use of dieldrin in Venezuela. *Bol. Of. Sanit. Panam.* **37**, 76–81 (in Spanish).
- Casarett, L. J., Fryer, G. C., Yauger, W. L., and Klemmer, H. W. (1968). Organochlorine pesticide residues in human tissue—Hawaii. *Arch. Environ. Health* **17**, 306–311.
- Case, R. A. M. (1945). Toxic effects of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT) in man. *Br. Med. J.* **2**, 842–845.
- Casida, J. E., and Lawrence, L. J. (1985). Structure–activity correlations for interactions of bicyclic phosphorus esters and some polychlorocycloalkane and pyrethroid insecticides with brain-specific *t*-butylbicyclic phosphorothionate receptor. *Environ. Health Perspect.* **61**, 123–132.
- Casida, J. E., Holmstead, R. L., Khalifa, S., Knox, J. R., Ohsawa, T., Palmer, K. J., and Wong, R. Y. (1974). Toxaphene insecticide: A complex biodegradable mixture. *Science* **183**, 520–521.
- Cassidy, W., Fisher, A. J., Peden, J. D., and Parry-Jones, A. (1967). Organochlorine pesticide residues in human fats from Somerset. *Mon. Bull. Minist. Health Public Health Lab. Serv. (G.B.)* **26**, 2–6.
- Cattabeni, F., Pastorello, M. C., and Eli, M. (1983). Convulsions induced by lindane and the involvement of the GABAergic system. *Arch. Toxicol. Suppl.* **6**, 244–249.
- Cecil, H. C., Harris, S. J., Bitman, J., and Reynolds, P. (1975). Estrogenic effects and liver microsomal enzyme activity of technical methoxychlor and technical 1,1-trichloro-2,2-bis(p-chlorophenyl)ethane in sheep. *J. Agric. Food Chem.* **23**, 401–403.
- Cerey, K., Izakovic, V., and Ruttkay-Nedecká, J. (1973). Effect of heptachlor on dominant lethality and bone marrow in rats. *Mutat. Res.* **21**, 26.
- Chadwick, R. W., and Copeland, M. F. (1985). Investigation of HCB as a metabolite from female rats treated daily for 6 days with lindane. *J. Anal. Toxicol.* **9**, 262–266.
- Chadwick, R. W., and Freal, J. J. (1972a). The identification of five unreported lindane metabolites recovered from rat urine. *Bull. Environ. Contam. Toxicol.* **7**, 137–146.
- Chadwick, R. W., and Freal, J. J. (1972b). Comparative acceleration of lindane metabolism to chlorophenols by pretreatment of rats with lindane or with DDT and lindane. *Food Cosmet. Toxicol.* **10**, 789–795.
- Chadwick, R. W., Cranmer, F. L., and Peoples, A. J. (1971a). Comparative stimulation of  $\gamma$ -HCH metabolism by pretreatment of rats with  $\gamma$ -HCH, DDT, and DDT +  $\gamma$ -HCH. *Toxicol. Appl. Pharmacol.* **18**, 685–695.
- Chadwick, R. W., Cranmer, M. F., and Peoples, A. J. (1971b). Metabolic alterations in the squirrel monkey induced by DDT administration and ascorbic acid deficiency. *Toxicol. Appl. Pharmacol.* **20**, 308–318.
- Chadwick, R. W., Peoples, A. J., and Cranmer, M. F. (1972). The effect of ascorbic acid deficiency and protein quality on stimulation of hepatic microsomal enzymes in guinea pigs. *Toxicol. Appl. Pharmacol.* **22**, 308–309.
- Chadwick, R. W., Linko, R. S., Freal, J. J., and Robbins, A. L. (1975). The effect of age and long-term low-level DDT exposure on the response to enzyme induction in the rat. *Toxicol. Appl. Pharmacol.* **31**, 469–480.
- Chadwick, R. W., Freal, J. J., Sovocool, G. W., Bryden, C. C., and Copeland, M. F. (1978a). The identification of three previously unreported lindane metabolites from mammals. *Chemosphere* **7**, 633–640.
- Chadwick, R. W., Copeland, M. F., and Chadwick, C. J. (1978b). Enhanced pesticide metabolism, a previously unreported effect of dietary fibre in mammals. *Food Cosmet. Toxicol.* **16**, 217–225.
- Chadwick, R. W., Copeland, M. F., Mole, M. L., Nesnow, S., and Cook, N. (1981). Comparative effect of pretreatment with phenobarbital, Aroclor 1254 and  $\beta$ -naphthoflavone on the metabolism of lindane. *Pestic. Biochem. Physiol.* **15**, 120–136.
- Chadwick, R. W., Chuong, L. T., and Williams, K. (1985). Dehydrogenation: A previously unreported pathway of lindane metabolism in mammals. *Pestic. Biochem. Physiol.* **5**, 575–586.
- Chadwick, R. W., Copeland, M. F., Wolff, G. L., Cook, N., Whitehouse, D. A., and Mole, M. L. (1986). Effects of age and obesity on the metabolism of lindane by black *a/a*, yellow *A<sup>y</sup>/a* and pseudoagouti *A<sup>y</sup>/a* phenotypes of (YS  $\times$  VY)F<sub>1</sub> hybrid mice. *J. Toxicol. Environ. Health* **16**, 771–796.
- Chadwick, R. W., Copeland, M. F., Wolff, G. L., Stead, A. G., Mole, M. L., and Whitehouse, D. A. (1987). Saturation of lindane metabolism in chronically treated (YS  $\times$  VY)F<sub>1</sub> hybrid mice. *J. Toxicol. Environ. Health* **20**, 411–434.
- Chakravarti, H. S. (1965). Polyneuritis due to DDT. *J. Indian Med. Assoc.* **45**, 598–599.
- Chamberlain, J. (1971). The determination of urinary 6-oxygenated cortisol in evaluating liver function. *Clin. Chim. Acta* **34**, 269–271.
- Chambers, J. E., and Trevanthen, C. A. (1983). Effect of mirex, dechlorinated mirex derivatives and chlordecone on microsomal mixed-function oxidase activity and other hepatic parameters. *Toxicol. Lett.* **16**, 109–115.
- Chambers, J. E., and Yarbrough, J. D. (1979). Disposition and excretion of mirex, 2,8-dihydromirex and 5,10-dihydromirex by adult rats. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **38**, 266.
- Chambers, J. E., Case, R. S., Alley, E. G., and Yarbrough, J. D. (1982). Short-term fate of mirex and 2,8-dihydromirex in rats. *J. Agric. Food Chem.* **30**, 378–382.
- Chambers, P. L. (1982). A possible site of action of dieldrin in the brain. *Arch. Toxicol. Suppl.* **5**, 112–115.
- Chandar, N., and Nagarajan, B. (1984). Induction of  $\gamma$ -glutamyltranspeptidase by hexachlorocyclohexane. *Biochem. Int.* **8**, 41–48.
- Chandurkar, P. S., and Matsumura, F. (1979). Metabolism of toxaphene components in rats. *Arch. Environ. Contam. Toxicol.* **8**, 1–24.
- Charles, A. K., Rosenbaum, D. P., Ashok, L., and Abraham, R. (1985). Uptake and disposition of mirex in hepatocytes and subcellular fractions in CD1 mouse liver. *J. Toxicol. Environ. Health* **15**, 395–403.
- Chase, H. P., Barnett, S. E., Welch, N. N., Bries, F. W., and Krassner, M. L. (1973). Pesticides and US farm labor families. *Rocky Mt. Med. J.* **70**, 27–31.
- Chen, P. H., Tilson, H. A., Marbury, G. D., Karoun, F., and Hong, J. J. (1985). Effect of chlordecone (Kepone) on the rat brain concentrations of 3-methoxy-4-hydroxyphenylglycol: Evidence for a possible involvement of the norepinephrine system in chlordecone-induced tremor. *Toxicol. Appl. Pharmacol.* **77**, 158–164.
- Chernoff, N., and Carver, B. D. (1976). Fetal toxicity of toxaphene in rats and mice. *Bull. Environ. Contam. Toxicol.* **15**, 660–664.
- Chernoff, N., and Rogers, E. H. (1976). Fetal toxicity of Kepone in rats and mice. *Toxicol. Appl. Pharmacol.* **38**, 189–194.
- Chernoff, N., Kavlock, R. J., Kathrein, J. R., Dunn, J. M., and Haseman, J. K. (1975). Prenatal effects of dieldrin and photodieldrin in mice and rats. *Toxicol. Appl. Pharmacol.* **31**, 302–308.
- Chernoff, N., Kavlock, R. J., Hanisch, R. C., Whitehouse, D. A., Gray, J. A., Gray, L. E., and Sovocool, G. W. (1979a). Perinatal toxicity of endrin in rodents. I. Fetotoxic effects of prenatal exposure in hamsters. *Toxicology* **13**, 155–165.
- Chernoff, N., Linder, R. E., Scott, T. M., Rogers, E. H., Carver, B. D., and Kavlock, R. J. (1979b). Fetotoxicity and cataractogenicity of mirex in rats and mice with notes on Kepone. *Environ. Res.* **18**, 257–269.
- Chhabra, R. S., and Fouts, J. R. (1974). Stimulation of hepatic drug metabolizing enzymes by DDT, polycyclic hydrocarbons or phenobarbital in adrenalectomized or castrated mice. *Toxicol. Appl. Pharmacol.* **28**, 465–476.
- Chin, Y., and T'Ant, C. (1946). The effect of DDT on cutaneous sensation in man. *Science* **103**, 654.
- Chipman, J. K., and Walker, C. H. (1979). The metabolism of dieldrin and two of its analogues. The relationship between rates of microsomal metabolism and rates of excretion of metabolites in the male rat. *Biochem. Pharmacol.* **28**, 1337–1345.
- Chowdhury, A. R., Venkatakrishna-Bhatt, H., and Gautam, A. K. (1987). Testicular changes of rats under lindane treatment. *Bull. Environ. Contam. Toxicol.* **38**, 154–156.
- Christophers, A. J. (1969). Hematological effects of pesticides. *Ann. N.Y. Acad. Sci.* **160**, 352–355.
- Chu, I., Villeneuve, D. C., Secours, V., Becking, G. C., Viau, A., and Benoit, F. (1979). The absorption, distribution and excretion of photomirex in the rat. *Drug. Metab. Dispos.* **7**, 24–27.
- Chu, I., Villeneuve, D. C., Becking, G. C., Iverson, F., Ritter, L., Valli, V. E., and Reynolds, L. M. (1980a). Short-term study of the combined effects of mirex, photomirex, and Kepone with halogenated biphenyls in rats. *J. Toxicol. Environ. Health* **6**, 421–432.
- Chu, I., Villeneuve, D. C., Becking, G. C., and Viau, A. (1980b). Tissue distribution and elimination of 2,8-dihydromirex in the rat. *J. Toxicol. Environ. Health* **6**, 713–721.
- Chu, I., Villeneuve, D. C., Valli, V. E., Secours, V. E., and Becking, G. C. (1981a). Chronic toxicity of photomirex in the rat. *Toxicol. Appl. Pharmacol.* **59**, 268–278.
- Chu, I., Villeneuve, D. C., MacDonald, B. L., Secours, V. E., and Valli, V. E. (1981b). Reversibility of the toxicological changes induced by photomirex and mirex. *Toxicology* **21**, 235–250.
- Chu, I., Villeneuve, D. C., Secours, V. E., Valli, V. E., and Becking, G. C. (1981c). Effects of photomirex and mirex on reproduction in the rat. *Toxicol. Appl. Pharmacol.* **60**, 549–556.
- Chu, I., Villeneuve, D. C., Sun, C.-W., Secours, V., Procter, B., Arnold, E., Clegg, D., Reynolds, L., and Valli, V. E. (1986). Toxicity of toxaphene in the rat and beagle dog. *Fundam. Appl. Toxicol.* **7**, 408–418.
- Chu, I., Secours, V., Villeneuve, D. C., Valli, V. E., Nakamura, A., Colin, D., Clegg, D. J., and Arnold, E. P. (1988). Reproduction study of toxaphene in the rat. *J. Environ. Sci. Health, Part B* **23**, 101–126.
- Chung Hwang, E., and Van Woert, M. H. (1981). *p,p'*-DDT-induced alterations in brain serotonin metabolism. *Neurotoxicology* **2**, 649–657.
- Cianflone, D. J., Hewitt, W. R., Villeneuve, D. C., and Plaa, G. L. (1980). Role of biotransformation in the alterations of chloroform hepatotoxicity produced by Kepone and mirex. *Toxicol. Appl. Pharmacol.* **53**, 140–149.
- Cinotti, V. (1971). Poisoning with Radosan and Gamacid caused vertiginous disorders. *Srp. Arh. Celok. Lek.* **98**, 1213–1217 (in Serbian).
- Ciupe, R. (1976). Determination of BHC, *p,p'*-DDT, and *p,p'*-DDE in food and adipose tissue. *Igiena* **15**(2), 113–117 (in Romanian).
- Clapp, K. L., Nelson, D. M., Bell, J. T., and Rousek, E. J. (1971). A study of the effects of toxaphene on the hepatic cells of rats. *Proc. Annu. Meet.—Am. Soc. Anim. Sci., West. Sect.* **22**, 313–323.
- Clark, D. E., Ivie, G. W., and Camp, B. J. (1981). Effects of dietary hexachlorobenzene or *in vivo* biotransformation, residue deposition, and elimination of certain xenobiotics by rats. *J. Agric. Food Chem.* **29**, 600–608.
- Clemmesen, J., Fugelsang-Fredricksen, V., and Plum, C. M. (1974). Are anticonvulsants oncogenic? *Lancet* **1**, 705–707.
- Clifford, N. J., and Weil, J. (1972). Cortisol metabolism in persons occupationally exposed to DDT. *Arch. Environ. Health* **24**, 145–147.
- Clinico-Pathologic Conference (1955). Exposure to insecticides, bone marrow failure, gastrointestinal bleeding, and uncontrolled infections. *Am. J. Med.* **19**, 274–284.
- Clodi, P. H., and Schnack, H. (1959). An attempted suicide with gamma-hexachlorocyclohexane (Inexid). *Wien. Z. Inn. Med. Ihre Grenzgeb.* **40**, 414–417 (in German).
- Cobey, F. A., Taliaferro, L., and Haag, H. B. (1956). Effect of DDD and some of its derivatives on plasma 17-OH-corticosteroids in the dog. *Science* **123**, 140–141.
- Coble, Y., Hildebrandt, P., Davis, J., Raasch, F., and Curley, A. (1967). Acute endrin poisoning. *JAMA, J. Am. Med. Assoc.* **202**, 489–493.
- Cochran, R. C., and Wiedow, M. A. (1984). Chlordecone lacks estrogenic properties in the male rat. *Toxicol. Appl. Pharmacol.* **76**, 519–525.
- Cocisui, M., Aizicovici, H., Nistor, C., Unterman, H. W., Barbuta, R., and Gugles, E. (1976). Variation of the DDT and HCH contents of maternal milk in connection with food intake. *Igiena* **25**, 105–108 (in Romanian).
- Cohn, W. J., Blanke, R. V., Griffith, F. D., and Guzelian, P. S. (1976). Distribution and excretion of Kepone (KP) in humans. *Gastroenterology* **71**, A-8/901.
- Cohn, W. J., Boylan, J. J., Blanke, R. V., Fariss, B. S., Howell, J. R., and Guzelian, P. S. (1978). Treatment of chlordecone (Kepone) toxicity with cholestyramine. Results of a controlled trial. *N. Engl. J. Med.* **298**, 243–248.
- Cole, J. F., Klevay, L. M., and Zavon, M. R. (1970). Endrin and dieldrin: A comparison of hepatic excretion in the rat. *Toxicol. Appl. Pharmacol.* **16**, 547–555.
- Cole, L. M., and Casida, J. E. (1986). Polychlorocycloalkane insecticide-induced convulsions in mice in relation to disruption of the GABA-regulated chloride ionophore. *Life Sci.* **39**, 1855–1862.
- Collins, G. B., Holmes, D. C., and Hoodless, R. A. (1982). Organochlorine pesticide residues in human milk in Great Britain 1979–80. *Hum. Toxicol.* **1**, 425–431.
- Committee on Pesticides (1951). American Medical Association Council on Pharmacy and Chemistry report on pharmacologic and toxicologic aspects of DDT (chlorophenothane U.S.P.). *JAMA, J. Am. Med. Assoc.* **145**, 728–733.



- Cook, L. L., Gordon, C. J., Tilson, H. A., and Edens, F. W. (1987). Chordecone-induced effects on thermoregulatory processes in the rat. *Toxicol. Appl. Pharmacol.* **90**, 126-134.
- Cook, L. L., Edens, F. W., and Tilson, H. A. (1988a). Possible brainstem involvement in the modification of thermoregulatory processes by chlordecone in rats. *Neuropharmacology*, **27**, 871-879.
- Cook, L. L., Edens, F. W., and Tilson, H. A. (1988b). Pharmacological evaluation of central adrenergic involvement in chlordecone-induced hypothermia. *Neuropharmacology*, **27**, 881-887.
- Cooper, J. R., Vodicnik, M. J., and Gordon, J. H. (1985). Effects of perinatal Kepone exposure on sexual differentiation of the rat brain. *Neurotoxicology* **6**(1), 183-190.
- Cooper, R. L., Chadwick, R. W., Rehnberg, G. C., Goldman, J. M., Booth, K. C., Hein, J. F., and McElroy, W. K. (1989). Effect of lindane on hormonal control of reproductive function in the female rat. *Toxicol. Appl. Pharmacol.* **99**, 384-394.
- Copeland, M. F., and Chadwick, R. W. (1979). Bioisomerization of lindane in rats. *J. Environ. Pathol. Toxicol.* **2**, 737-749.
- Copeland, M. F., and Cranmer, M. F. (1974). Effects of *o,p'*-DDT on the adrenal gland and hepatic microsomal enzyme system of the beagle dog. *Toxicol. Appl. Pharmacol.* **27**, 1-10.
- Copeland, M. F., Chadwick, R. W., Cooke, N., Whitehouse, D. A., Hill, D. M. (1986). Use of  $\gamma$ -hexachlorocyclohexane (lindane) to determine the ontogeny of metabolism in the developing rat. *J. Toxicol. Environ. Health* **18**, 527-542.
- Coper, H., Herken, H., and Klempau, I. (1951). On the pharmacology and toxicology of chlorinated cyclohexane. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **212**, 463-479 (in German).
- Copplestone, J. F., Hunnegg, J. N., and Harrison, D. L. (1973). Insecticides in adult New Zealanders—a five year study. *N.Z. J. Sci.* **16**, 27-39.
- Costella, J. C., and Virgo, B. B. (1980). Is dieldrin-induced congenital inviability mediated by central nervous system hyperstimulation or by altered carbohydrate metabolism. *Can. J. Physiol. Pharmacol.* **58**, 633-637.
- Coulston, F. (1985). Reconsideration of the dilemma of DDT for the establishment of an acceptable daily intake. *Regul. Toxicol. Pharmacol.* **5**, 332-383.
- Coutselinis, A., Kentarchou, P., and Boukis, D. (1978). Concentration levels of endosulfan in biological material (report of three cases). *Forensic Sci.* **11**, 75.
- Cranmer, J. M., Cranmer, M. F., and Goad, P. T. (1984). Prenatal chlordane exposure: Effects on plasma corticosterone concentrations over the lifespan of mice. *Environ. Res.* **35**, 204-210.
- Cranmer, J. S., Avery, D. L., and Barnett, J. B. (1979). Altered immune competence of offspring exposed during development to the chlorinated hydrocarbon pesticide chlordane. *Teratology* **19**, 23A.
- Cranmer, M. F. (1970). Effect of diphenylhydantoin on storage of DDT in the rat. *Toxicol. Appl. Pharmacol.* **17**, 315.
- Cranmer, M. F. (1972). Absence of conversion of *o,p'*-DDT to *p,p'*-DDT in the rat. *Bull. Environ. Contam. Toxicol.* **7**, 121-124.
- Cranmer, M. F., Carroll, J. J., and Copeland, M. F. (1969). Determination of DDT and metabolites, including DDA, in human urine by gas chromatography. *Bull. Environ. Contam. Toxicol.* **4**, 214-223.
- Cranmer, M. F., Peoples, A., and Chadwick, R. (1972). Biochemical effects of repeated administration of *p,p'*-DDT on the squirrel monkey. *Toxicol. Appl. Pharmacol.* **21**, 98-101.
- Crouch, L. S., and Ebel, R. E. (1987). Influence of chlordecone and mirex exposure on benzo[a]pyrene metabolism of rat liver microsomes. *Xenobiotica* **17**, 25-34.
- Crouch, M. F., and Roberts, M. L. (1985). The effects of  $\gamma$ -hexachlorocyclohexane on amylase secretion and inositol phospholipid metabolism in mouse pancreatic acini. *Biochim. Biophys. Acta* **844**, 149-157.
- Crowder, L. A., and Dindal, E. F. (1974). Fate of  $^{36}\text{Cl}$ -toxaphene in rats. *Bull. Environ. Contam. Toxicol.* **12**, 320-327.
- Cueto, C., Jr. (1970). Cardiovascular effects of *o,p'*-DDD. *Ind. Med. Surg.* **39**, 31-32.
- Cueto, C., Jr., and Biros, F. J. (1967). Chlorinated insecticides and related materials in human urine. *Toxicol. Appl. Pharmacol.* **10**, 261-269.
- Cueto, C., Jr., and Brown, J. H. U. (1958). Biological studies on an adrenocorticolytic agent and the isolation of the active components. *Endocrinology (Baltimore)* **62**, 334-339.
- Cueto, C., Jr., and Hayes, W. J., Jr. (1962). The detection of dieldrin metabolites in human urine. *J. Agric. Food Chem.* **10**, 366-369.
- Cueto, C., Jr., and Moran, N. C. (1968). The circulatory effects of catecholamines and ouabain in glucocorticoid-deficient animals. *J. Pharmacol. Exp. Ther.* **164**, 31-44.
- Cummings, A. M., and Gray, L. E. (1987). Methoxychlor affects the decidual cell response of the uterus but not other progestational parameters in female rats. *Toxicol. Appl. Pharmacol.* **90**, 330-336.
- Cummings, J. G., Eidelman, M., Turner, V., Reed, D., Zee, K. T., and Cook, R. E. (1967). Residues in poultry tissues from low level feeding of five chlorinated hydrocarbon insecticides to hens. *J. Assoc. Off. Anal. Chem.* **50**, 418-425.
- Cunningham, R. E., and Hill, F. S. (1952). Convulsions and deafness following ingestion of DDT. *Pediatrics* **9**, 745-747.
- Curley, A., and Garretson, L. K. (1969). Acute chlordane poisoning. *Arch. Environ. Health* **18**, 211-215.
- Curley, A., and Kimbrough, R. (1969). Chlorinated hydrocarbon insecticides in plasma and milk of pregnant and lactating women. *Arch. Environ. Health* **18**, 156-164.
- Curley, A., Copeland, M. F., and Kimbrough, R. D. (1969). Chlorinated hydrocarbon insecticides in organs of stillborn and blood of newborn babies. *Arch. Environ. Health* **19**, 628-632.
- Curley, A., Jennings, R. W., Mann, H. T., and Sedlak, V. (1970). Measurement of endrin following epidemics of poisoning. *Bull. Environ. Contam. Toxicol.* **5**, 24-29.
- Curley, A., Burse, V. W., Jennings, R. W., Villanueva, E. C., Tomatis, L., and Akazaki, K. (1973). Chlorinated hydrocarbon pesticides and related compounds in adipose tissue from people of Japan. *Nature (London)* **242**, 338-340.
- Curtis, L. R., and Hoyt, D. (1984). Impaired biliary excretion of taurocholate associated with increased biliary tree permeability in mirex- or chordecone-pretreated rats. *J. Pharmacol. Exp. Ther.* **231**, 495-501.
- Curtis, L. R., and Mehendale, H. M. (1979). The effects of Kepone treatment on biliary excretion of xenobiotics in the male rat. *Toxicol. Appl. Pharmacol.* **47**, 295-303.
- Curtis, L. R., and Mehendale, H. M. (1980). Specificity of chlordecone-induced potentiation of carbon tetrachloride hepatotoxicity. *Drug Metab. Dispos.* **8**, 23-27.
- Curtis, L. R., and Mehendale, H. M. (1981). Hepatobiliary dysfunction and inhibition of adenosine triphosphatase activity of bile canaliculi-enriched fractions following *in vivo* mirex, photomirex, and chlordecone exposures. *Toxicol. Appl. Pharmacol.* **61**, 429-440.
- Curtis, L. R., Williams, W. L., and Mehendale, H. M. (1979). Potentiation of the hepatotoxicity of carbon tetrachloride following preexposure to chordecone (Kepone) in the male rat. *Toxicol. Appl. Pharmacol.* **51**, 283-293.
- Curtis, L. R., Thureson-Klein, A. K., and Mehendale, H. M. (1981). Ultrastructural and biochemical correlates of the specificity of chlordecone-potentiated carbon tetrachloride hepatotoxicity. *J. Toxicol. Environ. Health* **7**, 499-517.
- Czarski, Z., Checinski, S., and Berbec, W. (1967). A case of poisoning with chlorinated hydrocarbons from the insecticide Ditox. *Pol. Tyg. Lek.* **22**, 27-29 (in Polish).
- Czegledi-Janko, G. (1969). Residues of chlorinated hydrocarbons in the blood of inhabitants of Budapest in 1967-1968 with particular reference to lindane. *Z. Gesamte Hyg. Ihre Grenzgeb.* **15**, 766-761.
- Czegledi-Janko, G., and Avar, P. (1970). Occupational exposure to lindane: Clinical and laboratory findings. *Br. J. Ind. Med.* **27**, 283-286.
- Dacre, J. C. (1969). Residual metabolites of hexachlorocyclohexane in human adipose tissues. *Proc. Univ. Otago Med. Sch.* **47**(3), 74-76.
- Dadey, J. L., and Kammer, A. G. (1953). Chlordane intoxication: A report of a case. *JAMA, J. Am. Med. Assoc.* **153**, 723-725.
- Daerr, W., Kaukel, E., and Schmoldt, A. (1985). Hemoperfusion—a therapeutic alternative for early treatment of acute lindane poisoning. *Disch. Med. Wochenschr.* **110**, 1253-1255 (in German).
- Dalley, R. E., Walton, M. S., Beck, V., Leavens, C. L., and Klein, A. K. (1970). Excretion, distribution, and tissue storage of a  $^{14}\text{C}$ -labelled photoconversion product of  $^{14}\text{C}$ -dieldrin. *J. Agric. Food Chem.* **18**, 443-445.
- Dalley, R. E., Klein, A. K., Brouwer, E., Link, J. D., and Braunberg, R. C. (1972). Effect of testosterone on metabolism of  $^{14}\text{C}$ -photodieldrin in normal, castrated and oophorectomized rats. *J. Agric. Food Chem.* **20**, 371-376.
- Dale, W. E., and Quinby, G. E. (1963). Chlorinated insecticides in the body fat of people in the United States. *Science* **142**, 593-595.
- Dale, W. E., Gaines, T. B., Hayes, W. J., Jr., and Pearce, G. W. (1963). Poisoning by DDT: Relation between clinical signs and concentration in rat brain. *Science* **142**, 1474-1476.
- Dale, W. E., Copeland, M. F., and Hayes, W. J., Jr. (1965). Chlorinated insecticides in the body fat of people in India. *Bull. W. H. O.* **33**, 471-477.
- Dale, W. E., Copeland, M. F., Pearce, G. W., and Miles, J. W. (1966a). Concentration of *o,p'*-DDT in rat brain at various intervals after dosing. *Arch. Int. Pharmacodyn. Ther.* **162**, 40-43.
- Dale, W. E., Curley, A., and Cueto, C., Jr. (1966b). Hexane extractable chlorinated pesticides in human blood. *Life Sci.* **5**, 47-54.
- Dale, W. E., Curley, A., and Hayes, W. J., Jr. (1967). Determination of chlorinated insecticides in human blood. *Ind. Med. Surg.* **36**, 275-280.
- Damaskin, V. I. (1965). The extent of the accumulation of DDT in the human body in connection with its assimilation and food, and its toxic effect. *Gig. Sanit.* **30**, 109-111.
- Dangerfield, W. G. (1946). Toxicity of DDT to man. *Br. Med. J.* **1**, 27.
- Daniel, C. S., Agarwal, S., and Agarwal, S. S. (1986). Human red blood cell membrane damage by endosulfan. *Toxicol. Lett.* **32**, 113-118.
- Danopoulos, E., Melissinos, K., and Katsas, G. (1953). Serious poisoning by hexachlorocyclohexane. Clinical and laboratory observations on five cases. *Arch. Ind. Hyg. Occup. Med.* **8**, 582-587.
- Danowski, T. S., Sarver, H. E., Moses, C., and Boness, J. V. (1964). *o,p'*-DDD therapy in Cushing's syndrome and in obesity with cushingoid changes. *Am. J. Med.* **37**, 235-250.
- da Rocha e Silva, E. O. (1961). A case of hypersensitivity to chlorinated insecticides (DDT and BHC). *Arq. Hig. Saude Publica* **26**, 51-55 (in Portuguese).
- Datta, P. R. (1970). *In vitro* detoxication of *p,p'*-DDT via *p,p'*-DDE to *p,p'*-DDA in rats. *Ind. Med. Surg.* **39**, 190-194.
- Datta, P. R., and Nelson, M. F. (1970). *p,p'*-DDT detoxication by isolated perfused rat liver and kidney. *Ind. Med. Surg.* **39**, 195-198.
- Davey, R. J., and Johnson, L. A. (1974). Tissue residues, blood chemistry and physiological response of lindane-treated swine. *J. Anim. Sci.* **38**, 318-324.
- Davidow, B., and Frawley, J. P. (1951). Tissue distribution, accumulation, and elimination of the isomers of benzene hexachloride. *Proc. Soc. Exp. Biol. Med.* **76**, 780-783.
- Davidow, B., Hagan, E. C., and Radomski, J. L. (1951). A metabolite of chlordane in tissues of animals. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **10**, 291.
- Davies, D., and Mes, J. (1987). Comparison of the residue levels of some organochlorine compounds in breast milk of the general and indigenous Canadian populations. *Bull. Environ. Contam. Toxicol.* **39**, 743-749.
- Davies, G. M., and Lewis, I. (1956). Outbreak of food poisoning from bread made from chemically contaminated flour. *Br. Med. J.* **2**, 393-398.
- Davies, J. E., Edmundson, W. F., Schneider, N. J., and Cassidy, J. D. (1968). Problems of prevalence of pesticide residues in humans. *Pestic. Monit. J.* **2**(2), 80-85.
- Davies, J. E., Edmundson, W. F., Carter, C. H., and Barquet, A. (1969). Effect of anticonvulsant drugs on dichophane (D.D.T.) residues in man. *Lancet* **2**, 7-9.
- Davies, J. E., Didhia, H. V., Morgade, C., Barquet, A., and Maibach, H. I. (1983). Lindane poisonings. *Arch. Dermatol.* **119**, 142-144.
- Davis, K. J., and Fitzhugh, O. G. (1962). Tumorigenic potential of aldrin and dieldrin for mice. *Toxicol. Appl. Pharmacol.* **4**, 187-189.
- Davis, M. E., and Mehendale, H. M. (1980). Functional and biochemical correlates of chlordecone exposure and its enhancement of  $\text{CCl}_4$  hepatotoxicity. *Toxicology* **15**, 91-103.
- Davison, K. L. (1970a). Dieldrin accumulation in tissues of sheep. *J. Agric. Food Chem.* **18**, 1156-1160.
- Davison, K. L. (1970b). Growth, hemoglobin, body composition and vitamin A in sheep fed dieldrin. *J. Anim. Sci.* **31**, 567-575.
- Davison, K. L. (1973). Dieldrin  $^{14}\text{C}$  balance in rats, sheep and chickens. *Bull. Environ. Contam. Toxicol.* **10**, 16-24.
- Davison, K. L., Mollenhauer, H. H., and Younger, R. L. (1976). Mirex-induced hepatic changes in chickens, Japanese quail, and rats. *Arch. Environ. Contam. Toxicol.* **4**, 469-482.
- Davison, K. L., Feil, V. J., and Lamoureux, C. H. (1982). Methoxychlor metabolism in goats. *J. Agric. Food Chem.* **30**, 130-137.
- Davison, K. L., Lamoureux, C. H., and Feil, V. J. (1983). Methoxychlor metabolism in goats. 2. Metabolites in bile and movement through skin. *J. Agric. Food Chem.* **31**, 164-166.
- Dean, B. J., Doak, S. M. A., and Somerville, H. (1975). The potential mutagenicity of dieldrin (HEOD) in mammals. *Food Cosmet. Toxicol.* **13**, 317-323.
- Dean, M. E., Smeaton, T. C., and Stock, B. H. (1980). The influence of fetal and neonatal exposure to dichlorodiphenyltrichloroethane (DDT) on the testosterone status of neonatal male rat. *Toxicol. Appl. Pharmacol.* **53**, 315-322.
- de Bellini, Y., Cressely, J., Deluzarche, A., and Hazemann, A. (1977). Organochlorine pesticides in women's milk. *Ann. Falsif. Exp. Chim.* **70**, 567.
- de Campos, M., and Olszyna-Marzys, A. E. (1978). Contamination of human milk with chlorinated pesticides in Guatemala and in El Salvador. *Arch. Environ. Contam. Toxicol.* **8**, 43-58.
- Dedek, W., and Schmidt, R. (1972). Studies on transplacental transport and metabolism of  $^3\text{H}$ - and  $^{14}\text{C}$ -labelled DDT in pregnant mice under hunger stress. *Pharmazie* **27**, 294-297.
- Deema, P., Thompson, E., and Ware, G. W. (1966). Metabolism, storage and excretion of  $\text{C}^{14}$ -endosulfan in the mouse. *J. Econ. Entomol.* **59**, 546-550.
- de Fernicola, N. A. G. G., and de Azevedo, F. A. (1982). Serum levels of organochlorine insecticides in humans in São Paulo, Brazil. *Vet. Hum. Toxicol.* **24**, 91-93.
- de Fossey, B. M., Luton, S. P., and Bricaire, H. (1968). Our experience of *o,p'*-DDD in the treatment of hypercortisisms. *Ann. Endocrinol.* **29**, 93-102 (in French).
- Deichmann, W. B., and Keplinger, M. L. (1970). Protection against the acute effects of certain pesticides by pretreatment with aldrin, dieldrin, and DDT. In "Pesticides Symposia" (W. B. Deichman, J. L. Radomski, and R. A. Penalver, eds.), pp. 121-123. Halos and Associates, Miami, Florida.
- Deichmann, W. B., and MacDonald, W. E. (1976). Liver cancer deaths in the continental USA from 1930 to 1972. *Am. Ind. Hyg. Assoc. J.* **37**, 495-498.
- Deichmann, W. B., and MacDonald, W. E. (1977). Organochlorine pesticides and liver cancer deaths in the United States, 1930-1972. *Ecotoxicol. Environ. Saf.* **1**, 89-110.
- Deichmann, W. B., Witherup, S., and Kitzmiller, K. V. (1950). "The Toxicity of DDT. I. Experimental Observations." Kettering Lab., Cincinnati, Ohio.
- Deichmann, W. B., Keplinger, M. L., Sala, F., and Glass, E. (1967). Synergism among oral carcinogens. IV. The simultaneous feeding of four tumorigens to rats. *Toxicol. Appl. Pharmacol.* **11**, 88-103.
- Deichmann, W. B., Dressler, I., Keplinger, M., and McDonald, W. E. (1968). Retention of dieldrin in blood, liver and fat of rats fed dieldrin for six months. *Ind. Med. Surg.* **37**, 837-839.
- Deichmann, W. B., Keplinger, M. L., Dressler, I., and Sala, F. (1969). Retention of dieldrin and DDT in the tissues of dogs fed aldrin and DDT individually and as a mixture. *Toxicol. Appl. Pharmacol.* **14**, 205-213.
- Deichmann, W. B., MacDonald, W. E., Blum, E., Bevilacqua, M., Radomski, J., Keplinger, M. L., and Balkus, M. (1970). Tumorigenicity of aldrin, dieldrin, and endrin in the albino rat. *Ind. Med. Surg.* **39**, 426-434.
- Deichmann, W. B., MacDonald, W. E., and Cubit, D. A. (1971a). DDT tissue retention: Sudden rise induced by the addition of aldrin to a fixed DDT intake. *Science*, **172**, 275-276.
- Deichmann, W. B., MacDonald, W. E., Beasley, A. G., and Cubit, D.



- (1971b). Subnormal reproduction in beagle dogs induced by DDT and aldrin. *Ind. Med. Surg.* **40**, 10-20.
- Deichmann, W. B., MacDonald, W. E., and Cubit, D. A. (1975). Dieldrin and DDT in the tissues of mice fed aldrin and DDT for seven generations. *Arch. Toxicol.* **34**, 173-182.
- Deichmann, W. B., MacDonald, W. E., and Lu, F. C. (1978). Effects of chronic aldrin feeding in two strains of female rats and a discussion on the risks of carcinogens in man. *Dev. Toxicol. Environ. Sci.* **4**, 407-413.
- DeKraay, W. H. (1978). Pesticides and lymphoma in Iowa. *J. Iowa Med. Soc.* **68**, 50-53.
- Del Vecchio, V., and Leoni, V. (1967). Research on levels of chlorinated insecticides in biological material. Note II. Cl: Chlorinated insecticides in adipose tissue of some groups of the Italian population. *Nuovi Ann. Ig. Microbiol.* **18**, 107-128 (in Italian).
- De Matteis, F. (1973). Drug interactions in experimental hepatic porphyria. A model for the exacerbation by drugs of human variegate porphyria. *Enzyme* **16**, 266-275.
- Demeter, J., and Heyndrickx, A. (1978). Two lethal endosulfan poisonings in man. *J. Anal. Toxicol.* **2**, 68-74.
- Demeter, J., Heyndrickx, A., Timperman, J., Lefevere, M., and DeBeer, J. (1977). Toxicological analysis in a case of endosulfan suicide. *Bull. Environ. Contam. Toxicol.* **18**, 110-114.
- Denes, A. (1962). Food chemistry problems of chlorinated hydrocarbon residues. *Nahrung* **6**, 48-56 (in German).
- Denes, A. (1964). Investigation of chlorinated hydrocarbon residues in animal and vegetable fats. In "1963 Year Book." Institute of Nutrition, Budapest, Hungary (in Hungarian).
- Denes, A. (1966). Dieldrin residues in foodstuffs and biological material. In "1965 Year Book," pp. 47-49. Institute of Nutrition, Budapest, Hungary (in Hungarian).
- Den Tonkelaar, E. M., and Van Esch, G. J. (1974). No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. *Toxicology* **2**, 371-380.
- Dequidt, J., Erb, F., Brice, A., and Van Aerde, C. (1973). Accumulation and transformation of heptachlor by the rat. *Bull. Soc. Pharm. Lille* **4**, 153-163 (in French).
- D'Eramo, N., and Croce, E. (1960). Acute erythematous-bullous dermatitis caused by contact with aldrin. *Riv. Infert. Mal. Prof.* **47**, 534-537 (in Italian).
- Derbes, V. J., Dent, J. H., Forrest, W. W., and Johnson, M. F. (1955). Fatal chlordane poisoning. *JAMA, J. Am. Med. Assoc.* **158**, 1367-1369.
- D'Ercole, A. J., Arthur, R. D., Cain, J. D., and Barrentine, B. F. (1976). Insecticide exposure of mothers and newborns in a rural agricultural area. *Pediatrics* **57**, 869-874.
- Desaiah, D. (1980). Comparative effects of chlordane and mirex on rat cardiac ATPases and binding of [<sup>3</sup>H]-catecholamines. *J. Environ. Pathol. Toxicol.* **4**, 237-248.
- Desaiah, D. (1981). Interaction of chlordane with biological membranes. *J. Toxicol. Environ. Health* **8**, 719-730.
- Desaiah, D., Ho, I. K., and Mehendale, H. M. (1977a). Effects of Kepone and mirex on mitochondrial Mg<sup>2+</sup> ATPase activity in rat liver. *Toxicol. Appl. Pharmacol.* **39**, 219-228.
- Desaiah, D., Ho, I. K., and Mehendale, H. M. (1977b). Inhibition of mitochondrial Mg<sup>2+</sup> ATPase activity in isolated perfused rat liver by Kepone. *Biochem. Pharmacol.* **26**, 1155-1159.
- Desaiah, D., Mehendale, H. M., and Ho, I. K. (1978). Kepone inhibition of mouse brain synaptosomal ATPase activities. *Toxicol. Appl. Pharmacol.* **45**, 268-269.
- Desaiah, D., Gilliland, I. K., Ho, I. K., and Mehendale, H. M. (1980). Inhibition of mouse brain synaptosomal ATPases and ouabain binding by chlordane. *Toxicol. Lett.* **6**, 275-285.
- Desaiah, D., Chetty, C. S., and Prasada Rao, K. S. (1985). Chlordane inhibition of calmodulin activated calcium ATPase in rat brain synaptosomes. *J. Toxicol. Environ. Health* **16**, 189-195.
- Desbuquois, G., Lutier, J., and Lebretevillos, G. (1963). Acute fatal intoxication by ingestion of lindane and malathion by an infant. *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **24**, 409-411.
- Descotes, J. (1986). "Immunotoxicology of Drugs and Chemicals." Elsevier, Amsterdam.
- Desi, I. (1974). Neurotoxicological effect of small quantities of lindane. *Int. Arch. Arbeitsmed.* **33**, 153-162 (in German).
- Desi, I., and Major, M. (1972). Neurotoxic effect of small lindane doses in animal experiments. *Egeszsegudomány* **38**, 98-99 (in Hungarian).
- de Vlieger, M., Robinson, J., Baldwin, M. K., Crabtree, A. N., and van Dijk, M. C. (1968). The organochlorine insecticide content of human tissue. *Arch. Environ. Health* **17**, 759-767.
- Dewan, A., Gupta, S. K., Jani, J. P., and Kashyap, S. K. (1980). Effect of lindane on antibody response to typhoid vaccine in weanling rats. *J. Environ. Sci. Health, Part B* **B15**, 395-402.
- Dickson, J., Peet, R. L., Duffy, R. J., Bolton, J., Hilbert, B., and McGill, C. (1984). Heptachlor poisoning in horses and cattle. *Aust. Vet. J.* **61**, 331.
- Didenko, G. G., Chernov, O. V., and Gupalovich, T. D. (1973). Study of possible blastomogenic effects of gammon-BHCB (lindane). *Gig. Sanit.* **38**, 98-99 (in Russian).
- Dietz, D. D., and McMillan, D. E. (1978). Effects of mirex and Kepone on schedule controlled responding. *Pharmacologist* **20**, 225.
- Dietz, D. D., and McMillan, D. E. (1979). Comparative effects of mirex and Kepone on schedule-controlled behaviour in the rat. I. Multiple fixed-ratio 12-fixed interval 2 min schedule. *Neurotoxicology* **1**, 369-385.
- Dikshith, T. S. S., and Datta, K. K. (1972). Effect of intratesticular injection of lindane and endrin on the testes of rats. *Acta Pharmacol. Toxicol.* **31**, 1-10.
- Dikshith, T. S. S., and Datta, K. K. (1978). Endosulfan: Lack of cytogenetic effects in male rats. *Bull. Environ. Contam. Toxicol.* **20**, 826-833.
- Dikshith, T. S. S., Chandra, P., and Datta, K. K. (1973). Effect of lindane on the skin of albino rats. *Experientia* **29**, 684-685.
- Dikshith, T. S. S., Datta, K. K., Kushwah, H. S., and Raizada, R. B. (1978a). Histopathological and biochemical changes in guinea pigs after repeated dermal exposure to benzene hexachloride. *Toxicology* **10**, 55-66.
- Dikshith, T. S. S., Nath, G., and Datta, K. K. (1978b). Combined cytogenetic effects of endosulfan and metepa in male rats. *Indian J. Exp. Biol.* **16**, 1000-1002.
- Dikshith, T. S. S., Raizada, R. B., Shivastava, M. K., and Kaphalia, B. S. (1984). Response of rats to repeated oral administration of endosulfan. *Ind. Health* **22**, 295-304.
- Dillon, J. C., Martin, G. B., and O'Brien, H. T. (1981). Pesticide residues in human milk. *Food Cosmet. Toxicol.* **19**, 437-442.
- Ditraglia, D., Brown, D. P., Namekata, T., and Iverson, N. (1981). Mortality study of workers employed at organochlorine pesticide manufacturing plants. *Scand. J. Work Environ. Health* **7**, Suppl. 4, 140-146.
- Djonckheere, W., Steurbax, W., Verstraeten, R., and Kips, R. H. (1977). Residues of organochlorine pesticides in human fat in Belgium. *Meded. Fac. Landbouwwet. Rijksuniv. Gent* **42**, 1839-1847.
- Dobson, R. C., Fahey, J. E., Ballee, D. C., and Baugh, E. R. (1971). Reduction of chlorinated hydrocarbon residues in swine. *Bull. Environ. Contam. Toxicol.* **6**, 391-400.
- Doguchi, M., Wshio, F., Niwayama, K., and Nishida, K. (1971). Pesticide content of human female fat in a metropolitan area. *Annu. Rep. Tokyo Metrop. Res. Lab. Public Health* **22**, 131-133 (in Japanese).
- Doman, I. (1971). Thiodan poisoning in sheep. *Magy. Allatorv. Lapja* **26**, 342-343 (in Hungarian).
- Domanski, J. J., Nelson, L. A., Guthrie, F. E., Domanski, R. E., Mark, R., and Postlethwaite, R. W. (1977). Relation between smoking and levels of DDT and dieldrin in human fat. *Arch. Environ. Health* **32**, 196-199.
- Domenjoz, R. (1944). Experimental investigation with a new insecticide (Neocide Geigy): A contribution to the theory of action of contact poison. *Schweiz. Med. Wochenschr.* **74**, 952-958 (in German).
- Domenjoz, R. (1946a). On the biological action of a DDT-derivative. *Arch. Int. Pharmacodyn.* **73**, 128-146 (in German).
- Domenjoz, R. (1946b). Biological action of a few derivatives of DDT. *Helv. Chim. Acta* **29**, 1317-1322 (in French).
- Dommarco, R., Muccio, A. D., Camoni, I., and Gigli, B. (1987). Organochlorine pesticide and polychlorinated biphenyl residues in human milk from Rome (Italy) and surroundings. *Bull. Environ. Contam. Toxicol.* **39**, 919-925.
- Dorough, H. W., and Ivie, G. W. (1974). Fate of mirex-<sup>14</sup>C during and after a 28-day feeding period to a lactating cow. *J. Environ. Qual.* **3**, 65-67.
- Dorough, H. W., Huhtanen, K., Marshall, T. C., and Bryant, H. E. (1978). Fate of endosulfan in rats and toxicological considerations of apolar metabolites. *Pestic. Biochem. Physiol.* **8**, 241-252.
- Downey, W. K., Flynn, M. P., and Aherne, S. A. (1975). Organochlorine content of milks, dairy products and animal feed ingredients: Ireland 1971-1972. *J. Dairy Res.* **42**, 21-29.
- Draize, J. G., Nelson, A. A., and Calvery, H. O. (1944). The percutaneous absorption of DDT (2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane) in laboratory animals. *J. Pharmacol. Exp. Ther.* **82**, 159-166.
- Drummond, L., Gillanders, E. M., and Wilson, H. K. (1988). Plasma  $\gamma$ -hexachlorocyclohexane concentrations in forestry workers exposed to lindane. *Br. J. Ind. Med.* **45**, 493-497.
- Dubey, R. K., Beg, M. U., and Singh, J. (1984). Effects of endosulfan and its metabolites on rat liver mitochondrial respiration and enzyme activities in vitro. *Biochem. Pharmacol.* **33**, 3405-3410.
- Dubois, J. M., and Bergman, C. (1977). Asymmetrical currents and sodium currents in Ranvier nodes exposed to DDT. *Nature (London)* **266**, 741-742.
- Dubsky, H., Rittich, B., Sommerova, H., Marek, V., Hana, K., and Janoušek, S. (1977). Determination of chlorinated pesticides in food and human fat tissues. *Vet. Med. (Prague)* **22**, 629-633 (in Czech).
- Ducharme, P. L. P. (1957). "Electroencephalographic Study of Dieldrin." Symp. Acerca de Ciertos Aspectos del uso del dieldrin en Venezuela. Division de Malaria, Direccion de Salud Publica, Ministerio de Sanidad y Asistencia Social (in Spanish).
- Duggan, R. E. (1968). Residues in food and feed. Pesticide residue levels in food in the United States from July 1, 1963 to June 30, 1967. *Pestic. Monit. J.* **2**, 2-46.
- Dunayevskiy, G. A. (1972). The functional condition of the circulatory organs in workers involved in organochlorine compounds' manufacturing. *Gig. Tr. Prof. Zabol.* **16**, 48-50 (in Russian).
- Dupire, A., and Raucourt, M. (1943). A new insecticide: The hexachloride of benzene. *C. R. Seances Acad. Agric. Fr.* **29**, 470-472 (in French).
- Durham, W. F., Ortega, P., and Hayes, W. J., Jr. (1963). The effect of various dietary levels of DDT on liver function, cell morphology, and DDT storage in the rhesus monkey. *Arch. Int. Pharmacodyn. Ther.* **141**, 111-129.
- Durham, W. F., Armstrong, J. F., and Quinby, G. E. (1965). DDA excretion levels. *Arch. Environ. Health* **11**, 76-79.
- Ebel, R. E. (1982). Alterations in microsomal cytochrome P-450 catalyzed reactions as a function of chlordane (Kepone) induction. *Pestic. Biochem. Physiol.* **18**, 113-121.
- Ebel, R. E. (1984). Hepatic microsomal p-nitroanisole O-demethylase. Effects of chlordane or mirex induction in male and female rats. *Biochem. Pharmacol.* **33**, 559-564.
- Eckenhausen, F. W., Bennett, D., Beynon, K. I., and Elgar, K. E. (1981). Organochlorine pesticide concentration in perinatal samples from mother and babies. *Arch. Environ. Health* **36**, 81-92.
- Eckols, K., Williams, J., and Uphouse L. (1989). Effects of chlordane on progesterone receptors in immature and adult rats. *Toxicol. Appl. Pharmacol.* **100**, 506-516.
- Edmundson, W. F., Davies, J. E., and Hull, W. (1968). Dieldrin storage levels in necropsy adipose tissue from a South Florida population. *Pestic. Monit. J.* **2**, 86-89.
- Edmundson, W. F., Davies, J. E., Nachman, G. A., and Roeth, R. L. (1969a). p,p'-DDT and p,p'-DDE in blood samples of occupationally exposed workers. *Public Health Rep.* **84**, 53-58.
- Edmundson, W. F., Davies, J. E., Cranmer, M., and Nachman, G. A. (1969b). Levels of DDT and DDE in blood and DDA in urine of pesticide formulators following a single intensive exposure. *Ind. Med. Surg.* **38**, 145-150.
- Edmundson, W. F., Davies, J. E., and Cranmer, M. (1970). DDT and DDE in blood and urine of men exposed to 3 percent DDT aerosol. *Public Health Rep.* **85**, 457-463.
- Egan, H., Goulding, R., Ropburn, J., and Tatton, J. O'G. (1965). Organochlorine pesticide residues in human fat and human milk. *Br. Med. J.* **2**, 66-69.
- Egle, J. L., Jr., Gochberg, B. J., and Borzelleca, J. F. (1976). The distribution of <sup>14</sup>C-Kepone in the rat. *Pharmacologist* **18**, 195.
- Egle, J. L., Jr., Fernandez, S. B., Guzelian, P. S., and Borzelleca, J. F. (1978). Distribution and excretion of chlordane (Kepone) in the rat. *Drug. Metab. Dispos.* **6**, 91-95.
- Egle, J. L., Jr., Guzelian, P. S., and Borzelleca, J. F. (1979). Time course of the acute toxic effects of sublethal doses of chlordane (Kepone). *Toxicol. Appl. Pharmacol.* **48**, 533-536.
- Eichler, D., Heupt, W., and Paul, W. (1983). Comparative study on the distribution of  $\alpha$ - and  $\gamma$ -hexachlorocyclohexane in the rat with particular reference to the problem of isomerization. *Xenobiotica* **13**, 639-647.
- Eisler, M. (1968). Heptachlor: Toxicology and safety evaluation. *Ind. Med. Surg.* **37**, 840-844.
- El-Aaser, A.-B. A., Reid, E., and Stevenson, D. E. (1972). Alkaline phosphatase patterns in dieldrin-treated dogs. *Hoppe-Seyler's Z. Physiol. Chem.* **353**, 667-673.
- Eldefrawi, M. E., Sherby, S. M., Abalis, I. M., and Eldefrawi, A. T. (1985). Interactions of pyrethroid and cyclodiene insecticides with nicotinic acetylcholine and GABA receptors. *Neurotoxicology* **6**(2), 47-62.
- Eldridge, B. F. (1973). Repellents and impregnants for the control of body lice. *Sci. Publ.—Pan Am. Health Organ.* **263**, 177-178.
- Elgart, M. L., and Higdon, R. S. (1973). Pediculosis pubis of the scalp. *Arch. Dermatol.* **107**, 916-917.
- Eliason, B. C., and Posner, H. S. (1971). Reduced passage of carbon-14-dieldrin to the fetal rat by phenobarbital but not by eight other drugs or dieldrin. *Am. J. Obstet. Gynecol.* **110**, 943-947.
- Ely, T. D., MacFarlane, J. W., Galen, W. P., and Hine, C. H. (1967). Convulsions in Thiodan workers: A preliminary report. *J. Occup. Med.* **9**, 35-37.
- Embry, T. L., Morgan, D. P., and Roan, C. C. (1972). Search for abnormalities of heme synthesis and sympathoadrenal activity. *J. Occup. Med.* **14**, 918-921.
- End, D. W., Carchman, R. A., Ameen, R., and Dewey, W. L. (1979). Inhibition of rat brain mitochondrial calcium transport by chlordane. *Toxicol. Appl. Pharmacol.* **51**, 189-196.
- End, D. W., Carchman, R. A., and Dewey, W. L. (1981). Neurochemical correlates of chlordane neurotoxicity. *J. Toxicol. Environ. Health* **8**, 707-718.
- Engelbreton, K. A., and Davison, K. L. (1971). Dieldrin accumulation and excretion by rats fed phenobarbital and carbon. *Bull. Environ. Contam. Toxicol.* **6**, 391-400.
- English, D., Schell, M., Siakotos, A., and Gabig, T. G. (1986). Reversible activation of the neutrophil superoxide generating system by hexachlorocyclohexane: Correlation with effects on a sub-cellular superoxide-generating fraction. *J. Immunol.* **137**, 283-290.
- Engst, R., and Knoll, R. (1972). Organochlorine pesticide residues in human milk. *Pharmazie* **27**, 526-531 (in German).
- Engst, R., Knoll, R., and Nickel, B. (1967). Concentration of chlorinated hydrocarbons especially DDT and its metabolic DDE in human fat. *Pharmazie* **22**, 654-661 (in German).
- Epstein, S. S. (1978). Kepone—hazard evaluation. *Sci. Total Environ.* **9**, 1-62.
- Epstein, S. S., and Ozonoff, D. (1987). Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. *Teratogen. Carcinogen. Mutagen.* **7**, 527-540.
- Epstein, S. S., and Shafner, H. (1968). Chemical mutagens in the human environment. *Nature (London)* **219**, 385-387.
- Epstein, S. S., Arnold, E., Andrea, J., Bass, W., and Bishop, Y. (1972). Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. Appl. Pharmacol.* **23**, 288-325.
- Eriksson, P., and Nordberg, A. (1986). The effects of DDT, DDOH-palmitic acid, and a chlorinated paraffin on muscarinic receptors and the sodium-dependent choline uptake in the central nervous system of immature mice. *Toxicol. Appl. Pharmacol.* **85**, 121-127.
- Eriksson, P., Flakeborn, Y., Nordberg, A., and Slanina, P. (1984). Effects of



- DDT on muscarinic and nicotine-like binding sites in CNS of immature and adult mice. *Toxicol. Lett.* **22**, 329-334.
- Eroschenko, V. P. (1982). Surface changes in oviduct, uterus and vaginal cells of neonatal mice after estradiol-17 $\beta$  and the insecticide chlordane (Kepone) treatment: A scanning electron microscopic study. *Biol. Reprod.* **26**, 707-720.
- Eroschenko, V. P., and Mousa, M. A. (1979). Neonatal administration of insecticide chlordane and its effects on the development of the reproductive tract in the female mouse. *Toxicol. Appl. Pharmacol.* **49**, 151-159.
- Eroschenko, V. P., and Osman, F. (1986). Scanning electron microscopic changes in vaginal epithelium of suckling neonatal mice in response to estradiol or insecticide chlordane (Kepone) passage in milk. *Toxicology* **38**, 175-185.
- Erslev, A. J., and Wintrobe, M. M. (1962). Detection and prevention of drug-induced blood dyscrasias. *JAMA, J. Am. Med. Assoc.* **181**, 116-119.
- Ervin, M. G., and Yarbrough, J. D. (1985). Mirex-induced liver enlargement in rats is dependent upon an intact pituitary-adrenocortical axis. *Life Sci.* **36**, 139-145.
- Esaac, E. G., and Matsumura, F. (1980). Mechanisms of reductive dechlorination of DDT by rat liver microsomes. *Pestic. Biochem. Physiol.* **10**, 81-93.
- Eskenasy, J. J. (1972). Status epilepticus by dichlorodiphenyltrichloroethane and hexachlorocyclohexane poisoning. *Rev. Roum. Neurol.* **9**, 435-442 (in Romanian).
- Espinosa-Gonzalez, J., and Thiel, R. (1987). Insecticide residues in the milk of Panamanian mothers. *Rev. Med. Panama* **12**, 139-143 (in Spanish).
- Espir, M. L. E., Hall, J. W., Shirreffs, J. G., and Stevens, D. L. (1970). Impotence in farm workers using toxic chemicals. *Br. Med. J.* **1**, 423-425.
- Ewing, A. D., Kadry, A. M., and Dorough, H. W. (1985). Comparative disposition and elimination of chlordane in rats and mice. *Toxicol. Lett.* **26**, 233-239.
- Eyzaguirre, C., and Lilienthal, J. L., Jr. (1949). Veratrinic effects of pentamethylenetetrazol (Metrazol) and 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT) on mammalian neuromuscular function. *Proc. Soc. Exp. Biol. Med.* **70**, 272-275.
- Fabacher, D. L., and Hodgson, E. (1976). Induction of hepatic mixed-function oxidase enzymes in adult and neonatal mice by Kepone and mirex. *Toxicol. Appl. Pharmacol.* **38**, 71-77.
- Fagan, J. E. (1981). Henoch-Schönlein purpura and ( $\gamma$ )-benzene hexachloride. *Pediatrics* **67**, 310-311.
- Failing, F., Rimer, C., Wooley, R., Sandifer, S. H., Hutcheson, R. H. J., Saucier, J. W., Ward, C., and Kutz, F. W. (1976). Chlordane contamination of a municipal water system—Tennessee. *Morbid. Moral. Wkly. Rep.* **25**, 117.
- Fariss, M. W., Blanke, R. V., Boylan, J. J., King, S. T., and Guzelian, P. S. (1978). Reductive biotransformation of chlordane in man and rat. *Toxicol. Appl. Pharmacol.* **45**, 337.
- Fariss, M. W., Blanke, R. V., Saady, J. J., and Guzelian, P. S. (1980). Demonstration of major metabolic pathways for chlordane (Kepone) in humans. *Drug. Metab. Dispos.* **8**, 434-438.
- Farkas, I., Desi, I., and Klemen, T. (1968). The effect of DDT on the diet on the resting and loading electrocorticogram record. *Toxicol. Appl. Pharmacol.* **12**, 518-525.
- Farkas, I., Desi, I., and Klemen, T. (1969). Effect of orally consumed DDT on the rest and load EEG curves. *Egeszsegtudomány* **13**, 195-201 (in Hungarian).
- Fattah, K. M. A., and Crowder, L. A. (1980). Plasma membrane ATPases from various tissues of the cockroach (*Periplaneta americana*) and mouse influenced by toxaphene. *Bull. Environ. Contam. Toxicol.* **24**, 356-363.
- Fawcett, S. C., Bunyan, P. J., Huson, L. W., King, L. J., and Stanley, P. I. (1981). Excretion of radioactivity following the intraperitoneal administration of  $^{14}\text{C}$ -DDT,  $^{14}\text{C}$ -DDD,  $^{14}\text{C}$ -DDE and  $^{14}\text{C}$ -DDMU to the rat and Japanese quail. *Bull. Environ. Contam. Toxicol.* **27**, 386-392.
- Fawcett, S. C., King, L. F., Bunyan, P. J., and Stanley, P. I. (1987). The metabolism of  $^{14}\text{C}$ -DDT,  $^{14}\text{C}$ -DDD,  $^{14}\text{C}$ -DDE and  $^{14}\text{C}$ -DDMU in rats and Japanese quail. *Xenobiotica* **17**, 525-538.
- Feil, V. J., Hedde, R. D., Zaylskie, R. G., and Zachrisson, C. H. (1970). Dieldrin- $^{14}\text{C}$  metabolism in sheep: Identification of *trans*-6,7-dihydroxydieldrin and hydro-1,4-*endo*-5,8-*exo*-dimethanonaphthalene. *J. Agric. Food Chem.* **18**, 120-124.
- Feil, V. J., Lamoureux, C. H., Styrvoky, E., Zaylskie, R. G., Thacker, E. J., and Holman, G. M. (1973). Metabolism of *o,p'*-DDT in rats. *J. Agric. Food Chem.* **21**, 1072-1078.
- Feil, V. J., Lamoureux, C. H., and Zaylskie, R. G. (1975). Metabolism of *o,p'*-DDT in chickens. *J. Agric. Food Chem.* **23**, 382-388.
- Feldmann, R. J., and Maibach, H. I. (1970). Pesticide percutaneous penetration in man. *J. Invest. Dermatol.* **54**, 435-436.
- Feldmann, R. J., and Maibach, H. I. (1974). Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol.* **28**, 126-132.
- Fennah, R. G. (1945). Preliminary tests with DDT against insect pests of food crops in the Lesser Antilles. *Trop. Agric.* **22**, 126-132.
- Ferrigan, L. W., Hunter, C. G., and Stevenson, D. E. (1965). Observations on the effects of continued oral exposure of rats to dieldrin. *Food Cosmet. Toxicol.* **3**, 149-151.
- Ferry, D. G., Owen, D., and McQueen, E. G. (1972a). The effect of phenytoin on the binding of pesticides to serum proteins. *Proc. Univ. Otago Med. Sch.* **50**, 8-9.
- Ferry, D. G., Owen, D., Ballard, D. L., and McQueen, E. G. (1972b). Pesticides and serum proteins. *Proc. Univ. Otago Med. Sch.* **50**, 10-11.
- Finklea, J., Priester, L. E., Creason, J. P., Hauser, T., Hinners, T., and Hammer, D. I. (1972). Polychlorinated biphenyl residues in human plasma expose a major urban pollution problem. *Am. J. Public Health* **62**, 645-651.
- Finnegan, J. K., Hennigar, G. R., Smith, R. B., Jr., Larson, P. S., and Haag, H. B. (1955). Acute and chronic toxicity studies on 2,2-bis(p-ethylphenyl)-1,1-dichloroethane (Perthane). *Arch. Int. Pharmacodyn. Ther.* **103**, 404-418.
- Fischer, R. (1966). Toxic renal failure induced by the pesticide aldrin. *Muenchen. Med. Wochenschr.* **108**, 1379-1381 (in German).
- Fiserova-Bergerova, V., Radomski, J. L., Davies, J. E., and Davies, J. H. (1967). Levels of chlorinated hydrocarbon pesticides in human tissues. *Ind. Med. Surg.* **36**, 65-70.
- Fishbein, L. F. (1974). Chromatographic and biological aspects of DDT and its metabolites. *J. Chromatogr.* **98**, 177-251.
- Fishbein, W. I., White, J. V., and Isaacs, H. J. (1964). Survey of workers exposed to chlordane. *Ind. Med. Surg.* **33**, 726-727.
- Fisher, D. B., and Mueller, G. C. (1971). Gamma-hexachlorocyclohexane inhibits the initiation of lymphocyte growth by phytohemagglutinin. *Biochem. Pharmacol.* **20**, 2515-2518.
- Fishman, B. E., and Gianutsos, G. (1985). Inhibition of 4-aminobutyric acid (GABA) turnover by chlordane. *Toxicol. Lett.* **26**, 219-223.
- Fishman, B. E., and Gianutsos, G. (1987a). Differential effects of gamma-hexachlorocyclohexane (lindane) on pharmacologically-induced seizures. *Arch. Toxicol.* **59**, 397-401.
- Fishman, B. E., and Gianutsos, G. (1987b). Opposite effects of hexachlorocyclohexane (lindane) isomers on cerebellar cyclic GMP: Relation of cyclic GMP accumulation to seizure activity. *Life Sci.* **41**, 1703-1709.
- Fishman, B. E., and Gianutsos, G. (1988). CNS biochemical and pharmacological effects of the isomers of hexachlorocyclohexane (lindane) in the mouse. *Toxicol. Appl. Pharmacol.* **93**, 146-153.
- Fitzhugh, O. G. (1948). Use of DDT insecticides on food products. *Ind. Eng. Chem.* **40**, 704-705.
- Fitzhugh, O. G. (1970). A summary of a carcinogenic study of DDT in mice from Food and Drug Administration, USA. In "FAO/WHO 1969 Evaluations of Some Pesticide Residues in Foods," pp. 61-64. World Health Organ., Geneva.
- Fitzhugh, O. G., and Nelson, A. A. (1947). The chronic oral toxicity of DDT (2,2-bis-p-chlorophenyl-1,1,1-trichloroethane). *J. Pharmacol. Exp. Ther.* **89**, 18-30.
- Fitzhugh, O. G., and Nelson, A. A. (1951). Comparison of chronic effects produced in rats by several chlorinated hydrocarbon insecticides. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **10**, 295.
- Fitzhugh, O. G., Nelson, A. A., and Frawley, J. P. (1950). The chronic toxicities of technical benzene hexachloride and its alpha, beta, and gamma isomers. *J. Pharmacol. Exp. Ther.* **100**, 59-66.
- Fitzhugh, O. G., Nelson, A. A., and Quaife, M. L. (1964). Chronic oral toxicity of aldrin and dieldrin in rats and dogs. *Food Cosmet. Toxicol.* **2**, 551-562.
- Fitzloff, J. F., and Pan, J. C. (1984). Epoxidation of the lindane metabolite, beta-PCCH, by human- and rat-liver microsomes. *Xenobiotica* **14**, 599-604.
- Fitzloff, J. F., Portig, J., and Stein, K. (1982). Lindane metabolism by human and rat liver microsomes. *Xenobiotica* **12**, 197-202.
- Fletcher, T. E., Press, J. M., and Wilson, D. B. (1959). Exposure of spraymen to dieldrin in residual spraying. *Bull. W. H. O.* **20**, 15-25.
- Flodström, S., Wärngård, L., Hemming, H., Fransson, R., and Ahlberg, U. G. (1988). Tumour promotion related effects by the cyclodiene insecticide endosulfan studied in vitro and in vivo. *Pharmacol. Toxicol.* **62**, 230-235.
- Focardi, S., Fossi, C., Leonzio, C., and Romei, R. (1986). PCB congeners, hexachlorobenzene, and organochlorine insecticides in human fat in Italy. *Bull. Environ. Contam. Toxicol.* **36**, 644-650.
- Fonseca, M. I., Aguilar, J. S., Lopez, C., Garcia Fernandez, J. C., and De Robertis, E. (1986). Regional effect of organochlorine insecticides on cholinergic muscarinic receptors of rat brain. *Toxicol. Appl. Pharmacol.* **84**, 192-195.
- Food and Agriculture Organization (FAO). (1972). "Production Yearbook—1971." Vol. 25, pp. 499-537. Food Agric. Organ., Rome.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1965). "Evaluation of the Toxicity of Pesticide Residues in Food," Monograph prepared by the Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues, which met in Rome, 15-22 March 1965, WHO/Food Add./27.65. Food Agric. Organ./World Health Organ., Rome.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1968). "1967 Evaluations of Some Pesticide Residues in Food," Monograph prepared by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, which met in Rome, 4-11 December 1967, WHO/Food Add./68.30. Food Agric. Organ./World Health Organ., Rome.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1969). "1968 Evaluations of Some Pesticide Residues in Food," Monograph prepared by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues which met in Geneva, 9-16 December 1968, WHO/Food Add./69.35. Food Agric. Organ./World Health Organ., Geneva.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1971). "1970 Evaluations of Some Pesticide Residues in Food," Monograph prepared by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues which met in Rome, 9-16 November 1970, WHO/Food Add./71.42. Food Agric. Organ./World Health Organ., Rome.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1974). "1973 Evaluations of Some Pesticide Residues in Food," Monograph prepared by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues that met in Geneva from 26 November to 5 December 1973, WHO Pestic. Residues Ser., No. 3. Food Agric. Organ./World Health Organ., Geneva.
- Food and Agriculture Organization/World Health Organization (FAO/WHO). (1985). "Pesticide Residues in Food—1984: Report of the Joint Meeting on Pesticide Residues, Rome, 24 September-30 October 1984," FAO Plant Prod. Prot. Pap. No. 62. Food Agric. Organ./World Health Organ., Rome.
- Foster, T. S. (1968). Effect of some pesticides on the adrenal glands in the rat. *J. Biochem. (Tokyo)* **46**, 1115-1120.
- Foster, T. S. (1973). Evaluation of the possible estrogenic activity of methoxychlor in the chicken by means of feeding trials. *Bull. Environ. Contam. Toxicol.* **9**, 234-242.
- Fournier, M., Bernier, J., Flipo, D., and Krzystyniak, K. (1986). Evaluation of pesticide effect on humoral response to sheep erythrocytes and mouse hepatitis virus 3 by immunosorbent analysis. *Pestic. Biochem. Physiol.* **26**, 353-364.
- Fouse, B. L., and Hodgson, E. (1987). Effects of chlordane and mirex on the acute hepatotoxicity of acetaminophen in mice. *Gen. Pharmacol.* **18**, 623-630.
- Fowler, B. A. (1972). The morphologic effects of dieldrin and methyl mercuric chloride on pars recta segment of rat kidney proximal tubules. *Am. J. Pathol.* **69**, 163-178.
- Fox, G. R., and Virgo, B. B. (1985). The effects of phenobarbital, atropine, L- $\alpha$ -methylpapa, and DL-propranolol on dieldrin-induced hyperglycemia in the adult rat. *Toxicol. Appl. Pharmacol.* **78**, 342-350.
- Fox, G. R., and Virgo, B. B. (1986a). Relevance of hyperglycemia to dieldrin toxicity in suckling and adult rats. *Toxicology* **38**, 315-326.
- Fox, G. R., and Virgo, B. B. (1986b). Effects of dieldrin on hepatic carbohydrate metabolism in the suckling and adult rat. *Can. J. Physiol. Pharmacol.* **64**, 694-698.
- Francone, M. P., Mariani, F. H., and Demare, C. (1952). Clinical picture of intoxication by DDT. *Rev. Asoc. Med. Argent.* **6**, 56-59 (in Spanish).
- Frank, R., and Braun, H. E. (1984). Lindane toxicity to four-month-old calves. *Bull. Environ. Contam. Toxicol.* **32**, 533-536.
- Freal, J. J., and Chadwick, R. W. (1973). Metabolism of hexachlorocyclohexane to chlorophenols and effect of isomer pretreatment on lindane metabolism in rat. *J. Agric. Food Chem.* **21**, 424-427.
- French, M. C., and Jefferies, D. J. (1968). Disappearance of gamma BHC from avian liver after death. *Nature (London)* **219**, 164-166.
- French, M. C., and Jefferies, D. J. (1969). Degradation and disappearance of ortho, para isomer of technical DDT in living and dead avian tissues. *Science* **165**, 914-916.
- Friberg, L., and Maartensson, J. (1953). Case of pancytopenia after exposure to chlorophenothane and benzene hexachloride. *Arch. Ind. Hyg. Occup. Med.* **8**, 166-169.
- Friberg, R. D., and Dodson, V. N. (1966). Cytogenetic studies of rats injected with lindane. *Toxicol. Appl. Pharmacol.* **8**, 341.
- Fries, G. F., Marrow, G. S., Jr., Gordon, C. H., Dryden, L. P., and Hartman, A. M. (1970). Effect of activated carbon on elimination of organochlorine pesticides from rats and cows. *J. Dairy Sci.* **53**, 1632-1637.
- Fries, G. F., Marrow, G. S., Jr., Lester, J. W., and Gordon, C. H. (1971). Effects of microsomal enzyme inducing drugs on DDT and dieldrin elimination from cows. *J. Dairy Sci.* **54**, 364-368.
- Frings, H., and O'Tousa, J. E. (1950). Toxicity to mice of chlordane vapor and solutions administered cutaneously. *Science* **111**, 658-660.
- Frost, I., and Poulsen, E. (1959). Aldrin poisoning. *Ugeskr. Laeg.* **121**, 1406 (in Danish).
- Fry, D. R. (1964). Human dieldrin poisoning. *Lancet* **1**, 764.
- Fujimori, K., Benet, H., Mehendale, H. M., and Ho, I. K. (1982a). Comparison of brain discrete areas distributions of chlordane and mirex in the mouse. *Neurotoxicology* **3** (2), 125-130.
- Fujimori, K., Nabeshima, T., Ho, I. K., and Mehendale, H. M. (1982b). Effect of oral administration of chlordane and mirex on brain biogenic amines in mice. *Neurotoxicology* **3** (2), 143-148.
- Fukano, S., and Doguchi, M. (1977). PCT, BPC, and pesticide residues in human fat and blood. *Bull. Environ. Contam. Toxicol.* **17**, 613-617.
- Fukushima, D. K., Bradlow, H. L., and Hellman, L. (1971). Effects of *o,p'*-DDD on cortisol and 6 beta-hydroxycortisol secretion and metabolism in man. *J. Clin. Endocrinol. Metab.* **32**, 192-200.
- Fulfs, J. C., and Abraham, R. (1976). Effects of mirex and chloroquine on PCB-induced hepatic porphyria in the rat. *Toxicol. Appl. Pharmacol.* **37**, 119-120.
- Fulfs, J. C., Abraham, R., and Coulston, F. (1975). Comparative ultrastructural and cytochemical studies in livers of mice, rats, and monkeys fed various levels of mirex. *Toxicol. Appl. Pharmacol.* **33**, 130-131.
- Fuller, G. B., and Draper, S. W. (1975). Effect of mirex on induced ovulation in immature rats. *Proc. Soc. Exp. Biol. Med.* **148**, 414-417.
- Fuller, G. B., Draper, S. W., and Gowdy, W. P. (1973). Effect of mirex on induced ovulation in immature rats. *J. Anim. Sci.* **36**, 211.
- Furie, B., and Trubowitz, S. (1976). Insecticides and blood dyscrasias: Chlordane exposure and self-limited refractory megaloblastic anemia. *JAMA, J. Am. Med. Assoc.* **235**, 1720-1722.



- Gablík, J., Askari, E. M., and Yolen, N. (1973). DDT and immunological responses. I. Serum antibodies and anaphylactic shock in guinea pigs. *Arch. Environ. Health* **26**, 305-308.
- Gablík, J., Al-Zubaidy, T., and Askari, E. (1975). DDT and immunological responses. 3. Reduced anaphylaxis and mast cell populations in rats fed DDT. *Arch. Environ. Health* **30**, 81-84.
- Gaines, T. B. (1960). The acute toxicity of pesticides to rats. *Toxicol. Appl. Pharmacol.* **2**, 88-99.
- Gaines, T. B. (1969). Acute toxicity of pesticides. *Toxicol. Appl. Pharmacol.* **14**, 515-534.
- Gaines, T. B., and Kimbrough, R. D. (1970). Oral toxicity of mirex in adult and suckling rats, with notes on the ultrastructure of liver changes. *Arch. Environ. Health* **21**, 7-14.
- Galand, P., Mairesse, N., Degraef, C., and Rooryck, J. (1987). *o,p'*-DDT(1,1-trichloro-2-(*p*-chlorophenyl)-2-(*o*-chlorophenyl)ethane) is a purely estrogenic agonist in the rat uterus *in vivo* and *in vitro*. *Biochem. Pharmacol.* **36**, 397-400.
- Galasinska-Pomykol, I., and Stefanska-Sulik, E. (1974). Morphological analysis of cells of the subthalamic nucleus of guinea pigs treated with the pesticide "Alvit-55." *Med. Pr.* **25**, 27-37 (in Polish).
- Galasinska-Pomykol, I., Tarmas, J., and Stefanska-Sulik, E. (1974). Morphological pattern of hypothalamic neurosecretory centers during convulsive state induced by pesticides. *Endokrynol. Pol.* **25**, 193-204 (in Polish).
- Galigani, D., and Melis, R. (1958). Poisoning by synthetic insecticides. *Minerva Med.* **48**, 3753-3763 (in French).
- Gallagher, T. F., Fukushima, D. K., and Hellmann, L. (1962). The effect of ortho, para DDD on steroid hormone metabolites in adrenocortical carcinoma. *Metab., Clin. Exp.* **11**, 1155-1161.
- Gandolfi, O., Cheney, D. C., Hong, J., and Costa, E. (1984). On the neurotoxicity of chlordane: A role for  $\gamma$ -aminobutyric acid and serotonin. *Brain Res.* **303**, 117-123.
- Gannon, N., Link, R. R., and Decker, G. C. (1959). Insecticide residues in the milk of dairy cows fed insecticides in their daily ration. *J. Agric. Food Chem.* **7**, 829-832.
- Gardner, J. (1958). Pediculosis capitis in preschool and school children: Control with a shampoo containing gamma benzene hexachloride. *J. Pediatr.* **52**, 448-450.
- Garg, A., Kunwar, K., Das, N., and Gupta, P. K. (1980). Endosulfan intoxication: Blood glucose, electrolytes, Ca levels, ascorbic acid and glutathione in rats. *Toxicol. Lett.* **5**, 119-123.
- Garrett, R. M. (1947). Toxicity of DDT for man. *J. Med. Assoc. State Ala.* **17**, 74-76.
- Garrettson, L. K., and Curley, A. (1969). Dieldrin: Studies in a poisoned child. *Arch. Environ. Health* **19**, 814-822.
- Garrettson, L. K., Guzelian, P. S., and Blanke, R. V. (1985). Subacute chlordane poisoning. *J. Toxicol. Clin. Toxicol.* **22**, 565-571.
- Gawhary, A. S. (1972). The effects of 2,2-bis(para-chloro-phenyl) 1,1-dichloroethane (DDD) on choline acetylase of the thymus gland. *Biochem. Pharmacol.* **21**, 887-890.
- Gellert, R. J. (1978). Kepone, mirex, dieldrin, and aldrin: Estrogenic activity and the induction of persistent vaginal estrus and anovulation in rats following neonatal treatment. *Environ. Res.* **16**, 131-138.
- Gellert, R. J., and Wilson, C. (1979). Reproductive function in rats exposed prenatally to pesticides and polychlorinated biphenyls (PCB). *Environ. Res.* **18**, 437-443.
- Gellert, R. J., Heinrichs, W. L., and Swerdloff, R. S. (1972). DDT homologues: Estrogen-like effects on the vagina, uterus, and pituitary of the rat. *Endocrinology (Baltimore)* **91**, 1095-1100.
- Genina, S. A., Svetlaja, E. N., and Komarova, L. I. (1969). Blood levels of organic chlorine pesticides and some hematological indicators in people employed in applying pesticides from the air. In "The Hygiene of Application and the Toxicology of Pesticides and the Clinical Features of Pesticide Poisoning. A Collection of Papers," Issue No. 7, pp. 492-496. Vniigintoks, Kiev (in Russian).
- Georgian, I. (1975). The comparative cytogenic effects of aldrin and phosphamidon. *Mutat. Res.* **31**, 103-108.
- Gerberg, E. J. (1973). Head lice: Control and nit removal. *Sci. Publ.—Pan Am. Health Organ.* **263**, 196-198.
- Gerhart, J. M., Hong, J. L., Uphouse, L. L., and Tilson, H. A. (1982). Chordecone-induced tremor: Quantification and pharmacological analysis. *Toxicol. Appl. Pharmacol.* **66**, 234-243.
- Gerhart, J. M., Hong, J. L., and Tilson, H. A. (1983). Studies on the possible sites of chordecone-induced tremor in rats. *Toxicol. Appl. Pharmacol.* **70**, 382-389.
- Gerhart, J. M., Hong, J. S., and Tilson, H. A. (1985). Studies on the mechanism of chordecone-induced tremor in rats. *Neurotoxicology* **61** (1), 211-229.
- Gertig, H., Nowaczyk, W., and Sawicka, B. (1971a). The effect of aldrin, dieldrin, lindane, DDT, DDD, and DDE on the activity of aldrin, phosphatase. *Diss. Pharm. Pharmacol.* **23**, 541-543.
- Gertig, H., Nowaczyk, W., and Sierznat, M. (1971b). The effect of aldrin, dieldrin, lindane, DDT, DDD, and DDE on the activity of aspartate and alanine aminotransferase. *Diss. Pharm. Pharmacol.* **23**, 545-548.
- Ghiasuddin, S. M., and Matsumura, F. (1979). DDT inhibition of Ca-ATPase of the peripheral nerves of the American lobster. *Pestic. Biochem. Physiol.* **10**, 151-161.
- Gibson, J. R., Ivie, G. W., and Dorough, H. W. (1972). Fate of mirex and its major photodecomposition product in rats. *J. Agric. Food Chem.* **20**, 1246-1248.
- Gil, G. P., and Miron, B. F. (1949). Investigations of intoxication by DDT in man. *Med. Colon.* **14**, 459-470 (in French).
- Gillett, J. W. (1968). No effect level of DDT in induction of microsomal epoxidation. *J. Agric. Food Chem.* **16**, 295-297.
- Gillett, J. W., and Chan, T. M. (1968). Cyclo-diene insecticides as inducers, substrates and inhibitors of microsomal epoxidation. *J. Agric. Food Chem.* **16**, 590-593.
- Gillett, J. W., Chan, T. M., and Terriere, L. C. (1966). Interactions between DDT analogs and microsomal epoxidase systems. *J. Agric. Food Chem.* **14**, 540-545.
- Gingell, R., and Wallcave, L. (1974). Species differences in the acute toxicity and tissue distribution of DDT in mice and hamsters. *Toxicol. Appl. Pharmacol.* **28**, 385-394.
- Ginsburg, C. M., and Lowry, W. (1983). Absorption of gamma benzene hexachloride following application of Karell shampoo. *Pediatr. Dermatol.* **1**, 74-76.
- Ginsburg, C. M., Lowry, W., and Reisch, J. S. (1977). Absorption of lindane (gamma benzene hexachloride) in infants and children. *J. Pediatr.* **91**, 998-1000.
- Glass, W. I. (1975). Dieldrin poisoning: Case report. *N. Z. Med. J.* **81**, 202-203.
- Gleason, M. N., Gosselin, R. E., and Hodge, H. C. (1963). "Clinical Toxicology of Commercial Products: Acute Poisoning (Home and Farm)." Williams & Wilkins, Baltimore, Maryland.
- Gold, B., and Brunk, G. (1982). Metabolism of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane in the mouse. *Chem.-Biol. Interact.* **41**, 327-339.
- Gold, B., and Brunk, G. (1983). Metabolism of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane, and 1-chloro-2,2-bis(*p*-chlorophenyl)ethane in the hamster. *Cancer Res.* **43**, 2644-2647.
- Gold, B., and Brunk, G. (1984). A mechanistic study of the metabolism of 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD) to 2,2-bis(*p*-chlorophenyl)acetic acid (DDA). *Biochem. Pharmacol.* **33**, 979-982.
- Gold, B., and Brunk, G. (1986). The effect of subchronic feeding of 1,1-dichloro-2,2-bis(4'-chlorophenyl)ethane (DDE) on its metabolism in mice. *Carcinogenesis (London)* **7**, 1149-1153.
- Gold, B., Leuschen, T., Brunk, G., and Gingell, R. (1981). Metabolism of a DDT metabolite via chloroepoxide. *Chem.-Biol. Interact.* **35**, 159-176.
- Goldman, J. M., Cooper, R. L., Rehnberg, G. L., Hein, J. F., McElroy, W. K., and Gray, L. E. (1986). Effect of low subchronic doses of methoxy-chlor on the rat hypothalamic-pituitary reproductive axis. *Toxicol. Appl. Pharmacol.* **86**, 474-483.
- Goldman, M. (1981). The effect of a single dose of DDT on thyroid function in male rats. *Arch. Int. Pharmacodyn. Ther.* **252**, 327-334.
- Good, E. E., and Ware, G. W. (1969). Effects of insecticides on reproduction in the laboratory mouse. IV. Endrin and dieldrin. *Toxicol. Appl. Pharmacol.* **14**, 201-203.
- Good, E. E., Ware, G. W., and Miller, D. F. (1965). Effects of insecticides on reproduction in the laboratory mouse: Kepone. *J. Econ. Entomol.* **58**, 754-757.
- Gopalswamy, U. V., and Aiyar, A. S. (1984a). Biotransformation of lindane in the rat. *Bull. Environ. Contamin. Toxicol.* **32**, 148-156.
- Gopalswamy, U. V., and Aiyar, A. S. (1984b). Effects of lindane on liver mitochondrial function in the rat. *Bull. Environ. Contamin. Toxicol.* **33**, 106-113.
- Gorbach, S. G., Christ, O. E., Kellner, H. M., Kloss, G., and Boerner, E. (1968). Metabolism of endosulfan in milk sheep. *J. Agric. Food Chem.* **16**, 950-953.
- Gordienko, V. M., and Kozyrskii, V. G. (1970). The effect of *o,p'*-dichlorodiphenyldichloroethane on the ultrastructure of cells of the anterior lobe of the hypophysis in dogs. *Ark. Anat., Gistol. Embriol.* **58**, 49-57 (in Russian).
- Gordienko, V. M., and Kozyrskii, V. G. (1973). Alterations in the ultrastructure of the adrenal cortex of the dog after short-term and long-term administration of *o,p'*-DDD. *Ark. Anat. Gistol. Embriol.* **65**, 90-95 (in Russian).
- Gordienko, V. M., Bogomolets, Y. O., and Kozyrskii, V. G. (1972). Electron microscopic study of the dog thyroid gland following administration of different doses of *o,p'*-dichlorodiphenyldichloroethane (*o,p'*-DDD). *Tsitol. Genet.* **6**, 392-394 (in Russian).
- Gordienko, V. M., Kozyrskii, V. G., and Drozdovich, I. I. (1973). Response of the hypothalamo-hypophyseal system in the development of hypocorticism. *Ark. Anat. Gistol. Embriol.* **65**, 62-68 (in Russian).
- Gordon, H. T., and Welsh, J. H. (1948). The role of ions in axon surface reactions to toxic organic compounds. *J. Cell. Comp. Physiol.* **31**, 395-420.
- Goto, M., Hattori, M., and Miyagawa, T. (1972a). Contribution on ecological chemistry. Toxicity of alpha-BHC in mice. *Chemosphere* **1**, 153-154 (in German).
- Goto, M., Hattori, M., Miyagawa, T., and Enomoto, M. (1972b). Contribution on ecological chemistry. II. Hepatoma-formation in mice after administration of HCH-isomers in high doses. *Chemosphere* **1**, 279-282 (in German).
- Goursaud, J., Luquet, F. M., and Casalis, J. (1971). Pesticide residue contamination of human milk in the northern province of France and Pas-de-Calais. *Lait* **51**, 559-567 (in French).
- Gowdey, C. W., and Stavaky, G. W. (1955). A study of the autonomic manifestations seen in acute aldrin and dieldrin poisoning. *Can. J. Biochem. Physiol.* **33**, 272-282.
- Gowdey, C. W., Graham, A. R., Seguin, J. J., and Stavaky, G. W. (1954). The pharmacological properties of the insecticide dieldrin. *Can. J. Biochem. Physiol.* **32**, 498-503.
- Grabowski, C. T. (1981). The plasma proteins and colloid osmotic pressure of blood of rat fetuses prenatally exposed to mirex. *J. Toxicol. Environ. Health* **7**, 705-714.
- Grabowski, C. T., and Payne, D. B. (1980). An electrocardiographic study of cardiovascular problems in mirex-fed rat fetuses. *Teratology* **22**, 167-177.
- Grabowski, C. T., and Payne, D. B. (1983a). The causes of perinatal exposure of rats to the pesticide mirex. Part I. Pre-parturition observations of the cardiovascular system. *Teratology* **27**, 7-11.
- Grabowski, C. T., and Payne, D. B. (1983b). The causes of perinatal death induced by prenatal exposure of rats to the pesticide mirex. Part II. Postnatal observations. *J. Toxicol. Environ. Health* **11**, 301-315.
- Graca, I., Silva Fernandes, A. M. S., and Maurao, H. C. (1974). Organochlorine insecticide residues in human milk in Portugal. *Pestic. Monit. J.* **8**, 148-156.
- Gracheva, G. V. (1969). The possibility of DDT accumulation in the organism of persons not having occupational contact with it. *Fakty Vnesn. Sred. Ikh Znach. Zdorov'ya Naseleniya* **1**, 125-129 (in Russian).
- Gracheva, G. V. (1970). DDT excretion with the milk of nursing mothers occupationally unexposed to the effect of this insecticide. *Vopr. Pitan.* **29**, 75-78 (in Russian).
- Grave, K., and Hermring, G. (1951). On the toxicity of gamma-hexachlorocyclohexane. *Arch. Int. Pharmacodyn. Ther.* **85**, 64-72 (in German).
- Graillot, C., Gak, J.-C., Lancet, C., and Truhaut, R. (1975). Investigations on the states and mechanisms of toxic action of organochlorine insecticides. II. Study on the long-term toxic effects of DDT in the hamster. *Eur. J. Toxicol.* **8**, 353-359 (in French).
- Grant, E. L., Mitchell, R. H., West, P. R., Mazuch, L., and Ashwood-Smith, M. J. (1976). Mutagenicity and putative carcinogenicity tests of several polycyclic aromatic compounds associated with impurities of the insecticide methoxychlor. *Mutat. Res.* **40**, 225-228.
- Gray, L. E. (1982). Neonatal chlordane exposure alters behavioural sex differentiation in female hamsters. *Neurotoxicology* **3** (2), 67-80.
- Gray, L. E., Jr., Kavlock, R., Chernoff, N., Lawton, D., and Gray, J. (1979). The effects of endrin administration during gestation on the behavior of the golden hamster. *Toxicol. Appl. Pharmacol.* **48**, A200.
- Gray, L. E., Ostby, J., Ferrell, J., Rehnberg, G., Linder, R., Cooper, R., Goldman, J., Slott, V., and Laskey, J. (1989). A dose response analysis of methoxychlor-induced alterations of reproductive development and function in the rat. *Fundam. Appl. Toxicol.* **12**, 92-108.
- Greene, F. E., Stevens, J. T., Soliman, M. R. I., and Oberholser, K. A. (1974). Effects of perinatal dieldrin exposure on hepatic microsomal enzymes of immature and adult rats. *Toxicol. Appl. Pharmacol.* **29**, 128.
- Greer, E. S., Miller, D. J., Bruscatto, F. N., and Holt, R. L. (1980). Investigation of pesticide residues in human adipose tissue in the northeast Louisiana area. *J. Agric. Food Chem.* **28**, 76-78.
- Griffith, F. D., Jr., and Blanke, R. V. (1975). Pesticides in people. Blood organochlorine pesticide levels in Virginia residents. *Pestic. Monit. J.* **8**, 219-224.
- Grover, P. L., and Sims, P. (1965). The metabolism of  $\alpha$ -2,3,4,5,6-pentachlorocyclohex-1-ene and  $\gamma$ -hexachlorocyclohexane in rats. *Biochem. J.* **96**, 521-525.
- Gruffydd-Jones, T. J., Evans, R. J., Brown, P., and Sullivan, K. (1981). Dieldrin poisoning of cats after woodworm treatment. *Vet. Rec.* **108**, 540.
- Grzycki, S., and Zarebska, A. (1973). Histochemical studies on the liver cell after the administration of gamma-benzene hexachloride (lindane). *Z. Mikrosk.-Anat. Forsch.* **87**, 470-476 (in German).
- Grzycki, S., Czerny, K., and Zarebska, A. (1973). Studies on the functional topography of the hydrolytic enzymes in the epithelium of the convoluted renal tubules. *Acta Histochem.* **47**, 350-357 (in German).
- Gulko, A. G., Zimnitsa, N. I., Diskalenko, A. P., Chernokan, V. F., and Bubucha, V. F. (1978). Pesticide carriers among certain population groups of Moldavia. *Gig. Sanit.* **43**, 36-41 (in Russian).
- Gupta, P. C. (1975). Neurotoxicity of chronic chlorinated hydrocarbon insecticide poisoning—a clinical and electro-encephalographic study in man. *Indian J. Med. Res.* **63**, 601-605.
- Gupta, P. K. (1976). Endosulfan-induced neurotoxicity in rats and mice. *Bull. Environ. Contam. Toxicol.* **15**, 708-713.
- Gupta, P. K. (1978). Distribution of endosulfan in plasma and brain after repeated oral administration to rats. *Toxicology* **9**, 371-377.
- Gupta, P. K., and Chandra, S. V. (1975). The toxicity of endosulfan in rabbits. *Bull. Environ. Contam. Toxicol.* **14**, 513-519.
- Gupta, P. K., and Chandra, S. V. (1977). Toxicity of endosulfan after repeated oral administration to rats. *Bull. Environ. Contam. Toxicol.* **18**, 378-384.
- Gupta, P. K., and Ehrnebo, M. (1979). Pharmacokinetics of  $\alpha$ - and  $\beta$ -isomers of racemic endosulfan following intravenous administration in rabbits. *Drug Metab. Dispos.* **7**, 7-10.
- Gupta, P. K., and Gupta, R. C. (1977). Effect of endosulfan pretreatment on organ weights and on pentobarbital hypnosis in rats. *Toxicology* **7**, 283-288.
- Gupta, P. K., Chandra, S. V., and Saxena, D. K. (1978). Teratogenic and embryotoxic effects of endosulfan in rats. *Acta Pharmacol. Toxicol.* **42**, 150-152.
- Gutierrez, M. L., and Crooke, S. T. (1980). Mitotane (*o,p'*-DDD) *Cancer Treat. Rev.* **7**, 49-55.
- Guzelian, P. S. (1981). Therapeutic approaches for chlordane poisoning in humans. *J. Toxicol. Environ. Health* **8**, 757-766.
- Guzelian, P. S. (1982a). Chlordane poisoning: A case study in approaches for the detoxification of humans exposed to environmental chemicals. *Drug Metab. Rev.* **13**, 663-679.
- Guzelian, P. S. (1982b). Comparative toxicology of chlordane (Kepone) in



- humans and experimental animals. *Annu. Rev. Pharmacol. Toxicol.* **22**, 89-113.
- Guzelian, P. S. (1984). New approaches for treatment of humans exposed to a slowly excreted environmental chemical (chlordecone). *Z. Gastroenterol.* **22**, 16-20 (in German).
- Guzelian, P. S. (1985). Clinical evaluation of liver structure and function in humans exposed to halogenated hydrocarbons. *Environ. Health Perspect.* **60**, 159-164.
- Guzelian, P. S., Vranian, G., Boylan, J. J., Cohn, W. J., and Blanke, R. V. (1980). Liver structure and function in patients poisoned with chlordecone (Kepone). *Gastroenterology* **78**, 206-213.
- Haag, H. B., Finnegan, J. K., Larson, P. S., Dreyfuss, M. L., Main, R. J., and Riese, W. (1948). Comparative chronic toxicity for warm-blooded animals of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) and 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane (DDD). *Ind. Med. Surg.* **17**, 477-484.
- Hajjar, R. A., Hickey, R. C., and Samoan, N. A. (1975). Adrenal cortical carcinoma: A study of 32 patients. *Cancer (Philadelphia)* **35**, 549-554.
- Halacka, K., Kaki, J., and Vymetal, F. (1965). A reflection in human fat tissue of the extensive use of DDT. *Czech. Hyg.* **10**, 188-192 (in Czech).
- Hall, E. T. (1974). An apparent case of chlordane poisoning. *Bull. Environ. Contamin. Toxicol.* **12**, 555-561.
- Hallett, D. J., Khera, K. S., Stoltz, D. R., Chu, I., Villeneuve, D. C., and Trivett, G. (1978). Photomirex: Synthesis and assessment of acute toxicity, tissue distribution, and mutagenicity. *J. Agric. Food Chem.* **26**, 288-291.
- Halmi, K. A., and Lascari, A. D. (1971). Conversion of virilization to feminization in a young girl with adrenal cortical carcinoma. *Cancer (Philadelphia)* **27**, 931-935.
- Halpern, L. K., Woolridge, W. E., and Weiss, R. S. (1950). Appraisal of the toxicity of the gamma isomer of hexachlorocyclohexane in clinical usage. *Arch. Dermatol. Syphilol.* **62**, 648-650.
- Hamid, J., Sayeed, A., and McFarlane, H. (1974). The effect of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane (*o,p'*-DDD) on the immune response in malnutrition. *Bri. J. Exp. Pathol.* **55**, 94-100.
- Hamilton, H. E., Morgan, D. P., and Simmons, A. (1978). A pesticide (dieldrin)-induced immunohemolytic anemia. *Environ. Res.* **17**, 155-164.
- Hammond, B., Bahr, J., Dial, O., McConnel, J., and Metcalf, R. (1978). Reproductive toxicology of mirex and Kepone. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **37**, 501.
- Hammond, B., Katzenellenbogen, B. S., Krauthammer, N., and McConnell, J. (1979). Estrogenic activity of the insecticide chlordecone (Kepone) and interaction with uterine estrogen receptors. *Proc. Natl. Acad. Sci. U.S.A.* **76**, 6641-6645.
- Hanada, M., Yutani, C., and Miyaji, T. (1973). Induction of hepatoma in mice by benzene hexachloride. *Gann* **64**, 511-513.
- HANES II (1980). "Health and Nutrition Examination Survey II: Laboratory Findings of Pesticide Residues, National Survey." U.S. Environ. Prot. Agency. Washington, D.C.
- Hanig, J. P., Yoder, P. D., and Krop, S. (1976). Convulsions in weanling rabbits after a single topical application of 1% lindane. *Toxicol. Appl. Pharmacol.* **38**, 463-469.
- Hansell, M. M., and Ecobichon, D. J. (1975). The morphological effects of maternally administered phenobarbital and DDT on hepatic cell structure in young rats. *Toxicol. Appl. Pharmacol.* **33**, 144.
- Hara, A., Iwasaki, I., Nawa, H., Yoshioka, Y., and Yokoo, S. (1973). Organochlorine insecticide residues in the blood of pregnant women and in umbilical cord blood. *igaku no Ayumi* **84**, 79-80 (in Japanese).
- Harbison, R. B. (1973). DDT, heptachlor, chlordane, and parathion toxicity in adult, newborn, and phenobarbital-treated newborn rats. *Toxicol. Appl. Pharmacol.* **25**, 472-473.
- Harell, M., Shea, J. J., and Emmett, J. R. (1978). Bilateral sudden deafness following combined insecticide poisoning. *Laryngoscope* **88**, 1348-1351.
- Harr, J. R., Claeys, R. R., Bone, J. R., and McCorde, T. W. (1970a). Dieldrin toxicosis: Rat production. *Am. J. Vet. Res.* **31**, 181-189.
- Harr, J. R., Claeys, R. R., and Benedict, N. (1970b). Dieldrin toxicosis in rats: Long-term study of brain and vascular effects. *Am. J. Vet. Res.* **31**, 1853-1862.
- Harrington, J. M., Baker, E. L., Jr., Folland, D. S., Saucier, J. W., and Sandifer, S. H. (1978). Chlordane contamination of a municipal water system. *Environ. Res.* **15**, 155-159.
- Harris, C. J., Williford, E. A., Kemberling, S. R., and Morgan, D. P. (1969). Pesticide intoxications in Arizona. *Ariz. Med.* **26**, 872-876.
- Harris, S. J., Cecil, H. C., and Bitman, J. (1974). Effect of several dietary levels of technical methoxychlor on reproduction in rats. *J. Agric. Food Chem.* **22**, 969-973.
- Harrison, J. H., Mahoney, E. M., and Bennett, A. H. (1973). Tumors of the adrenal cortex. *Cancer (Philadelphia)* **32**, 1227-1235.
- Harrison, M. A., Nicholls, T. J., and Rousseaux, C. G. (1980). Lindane toxicity in lambs. *Aust. Vet. J.* **56**, 42.
- Harrison, R. D. (1975). Comparative toxicity of some selected pesticides in neonatal and adult rats. *Toxicol. Appl. Pharmacol.* **32**, 443-446.
- Hart, M. M., and Straw, J. A. (1971a). Effects of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane and puromycin on adrenocorticotrophic hormone-induced steroidogenesis and on amino acid incorporation in slices of dog adrenal cortex. *Biochem. Pharmacol.* **20**, 257-263.
- Hart, M. M., and Straw, J. A. (1971b). Studies on the site of action of *o,p'*-DDD in the dog adrenal cortex. I. Inhibition of ACTH-mediated pregnenolone synthesis. *Steroids* **17**, 559-574.
- Hart, M. M., and Straw, J. A. (1971c). Effect of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane. *Biochem. Pharmacol.* **20**, 1679-1688.
- Hart, M. M., and Straw, J. A. (1971d). Effect of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane in vivo on baseline and adrenocorticotrophic hormone-induced steroid production in dog adrenal slices. *Biochem. Pharmacol.* **20**, 1689-1691.
- Hart, M. M., Regan, R. L., and Adamson, R. H. (1973). The effect of isomers of DDD on the ACTH-induced steroid output, histology, and ultrastructure of the dog adrenal cortex. *Toxicol. Appl. Pharmacol.* **24**, 101-113.
- Hartgrove, R. W., Jr., Petrella, V. J., and Webb, R. E. (1972). Microsomal activity in endrin susceptible and resistant pine mice. *Toxicol. Appl. Pharmacol.* **22**, 298.
- Hartgrove, R. W., Jr., Hundley, S. G., and Webb, R. E. (1974). Comparative inductive effects of phenobarbital and endrin on liver microsomal activity in endrin-resistant and susceptible pine voles. *Toxicol. Appl. Pharmacol.* **29**, 92.
- Hartgrove, R. W., Jr., Hundley, S. G., and Webb, R. E. (1977). Characterization of the hepatic mixed function oxidase system in endrin-resistant and -susceptible pine voles. *Pestic. Biochem. Physiol.* **7**, 146-153.
- Hartwig, W., Massalski, W., Kasperlik-Zaluska, A., Migdalska, B., Szamato-wics, M., and Jakowicki, J. (1968). Hormonally active carcinoma of the adrenal cortex treated with *o,p'*-DDD. *Endokrynol. Pol.* **19**, 57-69 (in Polish).
- Hashemy-Tonkabony, S. E., and Fateminassab, F. (1977). Chlorinated pesticide residues in milk of Iranian nursing mothers. *J. Dairy Sci.* **60**, 1858-1860.
- Hashemy-Tonkabony, S. E., and Soleimani-Amin, M. J. (1978). Chlorinated pesticide residues in the bodyfat of people of Iran. *Environ. Res.* **16**, 419-422.
- Hassall, K. A. (1971). Reductive dechlorination of DDT: The effect of some physical and chemical agents on DDD production by pigeon liver preparations. *Pestic. Biochem. Physiol.* **1**, 259-266.
- Hathway, D. E., and Mallinson, A. (1964). Chemical studies in relation to convulsive conditions. Effect of Telodrin on the liberation and utilization of ammonia in rat brain. *Biochem. J.* **90**, 51-60.
- Hathway, D. E., Mallinson, A., and Akintonwa, D. A. A. (1965). Effects of dieldrin, picrotoxin and Telodrin on the metabolism of ammonia in brain. *Biochem. J.* **94**, 676-686.
- Hattula, M. L., Ikkala, J., Isomaki, M., Maatta, K., and Arstila, A. U. (1976). Chlorinated hydrocarbon residues (PCB and DDT) in human liver, adipose tissue, and brain in Finland. *Acta Pharmacol. Toxicol.* **39**, 545-554.
- Haun, E. C., and Cueto, C., Jr. (1967). Fatal toxaphene poisoning in a 9-month-old child. *Am. J. Dis. Child.* **113**, 616-618.
- Havkin-Frenkel, D., Rosen, J. D., and Gallo, M. A. (1983). Enhancement of hydroxyl radical formation in rat liver microsomes by mirex. *Toxicol. Lett.* **15**, 219-223.
- Hayashi, M. (1972a). Pollution of mothers' milk by organochlorine pesticides. *Jpn. J. Public Health* **19**, 437-441 (in Japanese).
- Hayashi, M. (1972b). Pesticide pollution of mother's milk. *J. Jpn. Med. Assoc.* **68**, 1281-1286 (in Japanese).
- Hayashi, M. (1973). Pollution of mothers' milk by organochlorine compounds. *Pediatrics* **14**, 527-531.
- Hayashi, M. (1974). Mothers' milk and environmental pollution. *J. Pediatr. Pract.* **37**, 1113-1119.
- Hayden, M. J., Muelling, R. J., Noonan, J. A., and Bosomworth, P. P. (1965). A report of endrin poisoning. *J. Ky. Med. Assoc.* **63**, 33-34.
- Hayes, W. J., Jr. (1957). Dieldrin poisoning in man. *Public Health Rep.* **72**, 1087-1091.
- Hayes, W. J., Jr. (1959a). Pharmacology and toxicology of DDT. In "DDT: The Insecticide Dichlorodiphenyl-Trichloroethane and Its Significance" (P. Müller, ed.), Vol. 2, pp. 9-247. Birkhaeuser, Basel.
- Hayes, W. J., Jr. (1959b). The toxicity of dieldrin to man. *Bull. W. H. O.* **20**, 891-912.
- Hayes, W. J., Jr. (1963). "Clinical Handbook on Economic Poisons: Emergency Information for Treating Poisoning." Public Health Serv. Publ. No. 476. U.S. Gov. Printing Office, Washington, D.C.
- Hayes, W. J., Jr. (1965). Review of the metabolism of chlorinated hydrocarbon insecticides especially in mammals. *Annu. Rev. Pharmacol.* **5**, 27-52.
- Hayes, W. J., Jr. (1969). Sweden bans DDT. *Arch. Environ. Health* **18**, 872.
- Hayes, W. J., Jr. (1974). Distribution of dieldrin following a single oral dose. *Toxicol. Appl. Pharmacol.* **28**, 485-492.
- Hayes, W. J., Jr. (1975). "Toxicology of Pesticides." Williams & Wilkins, Baltimore, Maryland.
- Hayes, W. J., Jr. (1976a). Mortality in 1969 from pesticides, including aerosols. *Arch. Environ. Health* **31**, 61-72.
- Hayes, W. J., Jr. (1976b). Dosage relationships associated with DDT in milk. *Toxicol. Appl. Pharmacol.* **38**, 19-28.
- Hayes, W. J., Jr., and Curley, A. (1968). Storage and excretion of dieldrin and related compounds. *Arch. Environ. Health* **16**, 155-162.
- Hayes, W. J., Jr., and Vaughn, W. K. (1977). Mortality from pesticides in the United States in 1973 and 1974. *Toxicol. Appl. Pharmacol.* **42**, 235-252.
- Hayes, W. J., Jr., Ferguson, F. F., and Cass, J. S. (1951). The toxicology of dieldrin and its bearing on field use of the compound. *J. Trop. Med.* **31**, 519-522.
- Hayes, W. J., Jr., Durham, W. F., and Cueto, C., Jr. (1956). The effect of known repeated oral doses of chlorophenothane (DDT) in man. *JAMA, J. Am. Med. Assoc.* **162**, 890-897.
- Hayes, W. J., Jr., Quinby, G. E., Walker, K. C., Elliott, J. W., and Upholt, W. M. (1958). Storage of DDT and DDE in people with different degrees of exposure to DDT. *AMA Arch. Ind. Health* **18**, 398-406.
- Hayes, W. J., Jr., Dale, W. E., and LeBreton, R. (1963). Storage of insecticides in French people. *Nature (London)* **199**, 1189-1191.
- Hayes, W. J., Jr., Dale, W. E., and Burse, V. W. (1965). Chlorinated hydrocarbon pesticides in the fat of people in New Orleans. *Life Sci.* **4**, 1611-1615.
- Hayes, W. J., Jr., Dale, W. E., and Pirkle, C. I. (1971). Evidence of safety of long-term, high, oral doses of DDT for man. *Arch. Environ. Health* **22**, 119-135.
- Heath, D. F., and Vandekar, M. (1964). Toxicity and metabolism of dieldrin in rats. *Br. J. Ind. Med.* **21**, 269-279.
- Hedde, R. D., Davison, K. L., and Robbins, J. D. (1970). Dieldrin-14-C metabolism in sheep: Distribution and isolation of urinary metabolites. *J. Agric. Food Chem.* **18**, 116-119.
- Hegarty, M. L., Glende, F. A., and Recknagel, R. O. (1986). Potentiation by chlordecone of the defect in hepatic microsomal calcium sequestration induced by carbon tetrachloride. *J. Biochem. Toxicol.* **1** (2), 73-78.
- Hegy, E., and Stota, Z. (1962). The nature of the allergen in the manufacture of hexachlorocyclohexane. *J. Invest. Dermatol.* **38**, 111-113.
- Heiberg, O. M., and Wright, H. N. (1955). Benzene hexachloride poisoning. *AMA Arch. Ind. Health* **11**, 457-458.
- Heinevetter, D., Lewerenz, H. J., Plass, R., and Macholz, R. (1984). Comparative studies on the effect of hexachlorocyclohexane (HCH) and HCH metabolites on ATPases in rats and mice. *Z. Gesamte Hyg. Ihre Grenzgeb.* **30**, 576-579 (in German).
- Heinevetter, D., Lewerenz, H. J., Plass, R., and Macholz, R. (1985). Effect of lindane and lindane metabolites on microsomal and mitochondrial ATPases *in vitro*. *J. Environ. Sci. Health, Part B* **20**, 539-558.
- Heinricks, W. J., Gellert, R. J., Bakke, J. L., and Lawrence, N. L. (1971). DDT administered to neonatal rats induces persistent estrus syndrome. *Science* **173**, 642-643.
- Hellman, L., Bradlow, H. L., and Zumoff, B. (1973). Decreased conversion of androgens to normal 17-ketosteroid metabolites as a result of treatment with *o,p'*-DDD. *J. Clin. Endocrinol. Metab.* **36**, 801-803.
- Helson, L., Wollner, N., Murphy, L., and Schwartz, M. K. (1971). Metastatic adrenal cortical carcinoma: Biochemical changes accompanying clinical regression during therapy with *o,p'*-DDD. *Clin. Chem. (Winston-Salem, N.C.)* **17**, 1191-1193.
- Henderson, G. L., and Woolley, D. E. (1969). Tissue concentrations of DDT: Correlation with neurotoxicity in young and adult rats. *Proc. West. Pharmacol. Soc.* **12**, 58-62.
- Henderson, G. L., and Woolley, D. E. (1970). Mechanisms of neurotoxic action of 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane (DDT) in immature and adult rats. *J. Pharmacol. Exp. Ther.* **175**, 60-68.
- Hendrickson, C. M., and Bowden, J. A. (1975). The *in vitro* inhibition of rabbit muscle lactate dehydrogenase by mirex and Kepone. *J. Agric. Food Chem.* **23**, 407-409.
- Herbst, M., Weisse, I., and Koellmer, H. (1975). A contribution to the question of the possible hepatocarcinogenic effects of lindane. *Toxicology* **4**, 91-96.
- Herken, H., and Klempau, I. (1950). Neurotropic effects of some hexachlorocyclohexanes. *Naturwissenschaften* **37**, 493-494 (in German).
- Herken, H., Kewitz, H., and Klempau, I. (1952a). Loss of effect of poison-induced seizures by hexachlorocyclohexane. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **215**, 217-230 (in German).
- Herken, H., Monnier, M., Coper, H., and Laue, H. (1952b). Inhibition of subcortical seizure potential caused by  $\beta$ -hexachlorocyclohexane. *Experientia* **8**, 432-434 (in German).
- Herman, P., Jacobs, M., Hughes, G., Smith, B., McClintock, B., Farrar, W., and Holder, W. (1975). Scabies—Florida, New Mexico. *Morbid. Mortal. Wkly. Rep.* **24**, 118-123.
- Herr, D. W., and Tilson, H. A. (1987). Modulation of *p,p'*-DDT-induced tremor by catecholaminergic agents. *Toxicol. Appl. Pharmacol.* **91**, 149-158.
- Herr, D. W., Hong, J. S., and Tilson, H. A. (1985). DDT-induced tremor in rats: Effects of pharmacological agents. *Psychopharmacology* **86**, 426-431.
- Herr, D. W., Hong, J. S., Chen, P., Tilson, H., and Harry, G. J. (1986). Pharmacological modification of DDT-induced tremor and hyperthermia in rat: Distributional factors. *Psychopharmacology* **89**, 278-283.
- Herr, D. W., Gallus, J. A., and Tilson, H. A. (1987). Pharmacological modification of tremor and enhanced acoustic startle by chlordecone and *p,p'*-DDT. *Psychopharmacology* **91**, 320-325.
- Herr, D. W., Mailman, R. B., and Tilson, H. A. (1989). Blockade of only spinal  $\alpha$ -adrenoceptors is insufficient to attenuate DDT-induced alterations in motor function. *Toxicol. Appl. Pharmacol.* **101**, 11-26.
- Herrera-Martache, A., Polo Villar, L. M., Jodral Villarejo, M., Pollo Villar, G., Mallor, J., and Pozo Lora, R. (1978). Organochlorine pesticides residues in human fat in Spain. *Rev. Sanid. Hig. Publica* **52**, 1125-1144 (in Spanish).
- Hesse, V., Gabrio, T., Kirst, E., and Plenert, W. (1981). Investigation of the contamination of women's milk, cow milk and butter in the DDR with chlorinated hydrocarbons. *Koinderarzth. Prax.* **49**, 292 (in German).
- Hewitt, W. R., Miyajima, H., Cote, M., and Plaa, G. L. (1979). Acute alteration of chloroform-induced hepato- and nephrotoxicity by mirex and Kepone. *Toxicol. Appl. Pharmacol.* **48**, 509-527.
- Heyndrickx, A., and Maes, R. (1969). The excretion of chlorinated hydrocarbon insecticides in human mother milk. *J. Pharm. Belg.* **9-10**, 459-463.
- Hidaka, K., Ohe, T., and Fujiwara, K. (1972). PCB and organochlorine pesticides in mother's milk. *igaku no Ayumi* **82**, 519-520 (in Japanese).



- Higginson, J. (1985). DDT: Epidemiological evidence. *IARC Sci. Publ.* **65**, 101-105.
- Hirasawa, F. and Takizawa, Y. (1989). Accumulation and declination of chlor-dane congeners in mice. *Toxicol. Lett.* **47**, 109-117.
- Ho, I. K., Fujimori, K., Huang, T. P., and Chang-Tusi, H. (1981). Neurochemical evaluation of chlordecone toxicity in the mouse. *J. Toxicol. Environ. Health* **8**, 701-706.
- Hochleitner, H. (1973). The epidemiology, clinics and treatment of scabies. *Wien. Klin. Wochenschr.* **85**, 197-202 (in German).
- Hodge, H. C., Maynard, E. A., Thomas, J. F., Blanchet, H. J., Jr., Wilt, W. G., Jr., and Mason, K. E. (1950). Short-term oral toxicity tests of methoxychlor (2,2-di-(p-methoxyphenyl)-1,1,1-trichloroethane) in rats and dogs. *J. Pharmacol. Exp. Ther.* **99**, 140-148.
- Hodge, H. C., Maynard, E. A., and Blanchet, H. J., Jr. (1952). Chronic oral toxicity tests of methoxychlor (2,2-di-(p-methoxyphenyl)-1,1,1-trichloroethane) in rats and dogs. *J. Pharmacol. Exp. Ther.* **104**, 60-66.
- Hodge, H. C., Maynard, E. A., Downs, W. L., Ashton, J. K., and Salerno, L. (1966). Tests on mice for evaluating carcinogenicity. *Toxicol. Appl. Pharmacol.* **9**, 583-596.
- Hoffman, D. G., Worth, H. M., Emmerson, J. L., and Anderson, R. C. (1970). Stimulation of hepatic drug-metabolizing enzymes by chlorophenothane (DDT): The relationship to liver enlargement and hepatotoxicity in the rat. *Toxicol. Appl. Pharmacol.* **16**, 171-178.
- Hoffman, D. L., and Mattox, V. R. (1972). Treatment of adrenocortical carcinoma with *o,p'*-DDD. *Med. Clin. North Am.* **56**, 999-1012.
- Hoffman, I., and Lendle, L. (1948). The mode of action of a new insecticide. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **205**, 223-242 (in German).
- Hoffman, W. S., Fishbein, W. I., and Andelman, M. B. (1964). The pesticide content of human fat tissue. *Arch. Environ. Health* **9**, 387-394.
- Hoffman, W. S., Adler, H., Fishbein, W. I., and Bauer, F. C. (1967). Relation of pesticide concentration in fat to pathological changes in tissues. *Arch. Environ. Health* **15**, 758-765.
- Hoffman, R., Erzberger, P., Frank, W., and Ristow, H. (1980). Increased phosphatidylinositol synthesis in rat embryo fibroblasts after growth stimulation and its inhibition by  $\delta$ -hexachlorocyclohexane. *Biochim. Biophys. Acta* **618**, 282-292.
- Hofvander, Y., Hagman, U., Linder, C. E., Vaz, R., and Slorach, S. A. (1981). WHO collaborative breast feeding study. I. Organochlorine contaminants in individual samples of Swedish human milk, 1978-1979. *Acta Paediatr. Scand.* **70**, 3-8.
- Hokin, M. R., and Brown, D. F. (1969). Inhibition by gamma-hexachlorocyclohexane of acetylcholine-stimulated phosphatidylinositol synthesis in cerebral cortex slices and of phosphatidic acid-inositol transferase in cerebral cortex particulate fractions. *J. Neurochem.* **16**, 475-483.
- Holian, A., Marchiarullo, M. A., and Stickle, D. F. (1984).  $\gamma$ -Hexachlorocyclohexane activation of alveolar macrophage phosphatidylinositol cycle, calcium mobilization and  $O_2^-$  production. *FEBS Lett.* **176**, 151-154.
- Holmstead, R. L., Khalifa, S., and Casida, J. E. (1974). Toxaphene composition analyzed by combined gas chromatography-chemical-ionization mass spectrometry. *J. Agric. Food Chem.* **22**, 939-944.
- Hong, J. S., and Ali, S. F. (1982). Chlordecone (Kepone®) exposure in the neonate selectively alters brain and pituitary endorphin levels in prepubertal and adult rats. *Neurotoxicology* **3** (2), 111-117.
- Hong, J. S., Tilson, H. A., Uphouse, L. L., Gerhart, J., and Wilson, W. E. (1984). Effects of chlordecone exposure on brain neurotransmitters: Possible involvement of the serotonin system in chlordecone-elicited tremor. *Toxicol. Appl. Pharmacol.* **73**, 336-344.
- Hong, J. S., Hudson, P. M., Yoshikawa, K., Ali, S. F., and Mason, G. A. (1985). Effect of chlordecone administration on brain and pituitary peptide systems. *Neurotoxicology* **6** (1), 167-182.
- Hong, J. S., Herr, D. W., Hudson, P. M., and Tilson, H. A. (1986). Neurochemical effects of DDT in rat brain in vivo. *Arch. Toxicol., Suppl.* **9**, 14-26.
- Hoogendam, I., Versteeg, J. P. J., and de Vlieger, M. (1962). Electroencephalograms in insecticide toxicity. *Arch. Environ. Health* **40**, 86-94.
- Hoogendam, I., Versteeg, J. P. J., and de Vlieger, M. (1965). Nine years' toxicity control in insecticide plants. *Arch. Environ. Health* **10**, 441-448.
- Hooper, N. K., Ames, B. N., Saleh, M. A., and Casida, J. E. (1979). Toxaphene, a complex mixture of polychloroterpenes and a major insecticide, is mutagenic. *Science* **205**, 591-593.
- Hori, S., and Kashimoto, T. (1974). Transfer of beta-BHC from mother to suckling mouse. *J. Food Hyg. Soc. Jpn.* **15**, 446-450 (in Japanese).
- Horn, H. J., Bruce, R. B., and Paynter, O. E. (1955). Toxicology of chlorobenzilate. *J. Agric. Food Chem.* **3**, 752-756.
- Homabrook, R. W., Dymont, P. G., Gomes, E. D., and Wiseman, J. S. (1972). DDT residues in human milk from New Guinea natives. *Med. J. Aust.* **1**, 1297-1300.
- Hoskins, B., and Ho, I. K. (1982). Chlordecone-induced alterations in content and subcellular distribution of calcium in mouse brain. *J. Toxicol. Environ. Health* **9**, 535-544.
- Hosler, J., Tschanz, C., Hignite, C. E., and Azarnoff, D. C. (1980). Topical application of lindane cream (Kwell) and antipyrine metabolism. *J. Invest. Dermatol.* **74**, 51-53.
- Houston, J. E., Mutter, L. C., Blanke, R. V., and Guzelian, P. S. (1981). Chlordecone alcohol formation in the Mongolian gerbil (*Meriones uguiculatus*): A model for human metabolism of chlordecone (Kepone). *Fundam. Appl. Toxicol.* **1**, 293-298.
- Hrdina, P. D., Singhal, R. L., Peters, D. A. V., and Ling, G. M. (1973). Some neurochemical alterations during acute DDT poisoning. *Toxicol. Appl. Pharmacol.* **25**, 276-288.
- Hrdina, P. D., Singhal, R. L., and Peters, D. A. V. (1974). Changes in brain biogenic amines and body temperature after cyclodiene insecticides. *Toxicol. Appl. Pharmacol.* **29**, 119.
- Hrdina, P. D., Singhal, R. L., and Ling, G. M. (1975). DDT and related hydrocarbon insecticides: Pharmacological basis of their toxicity in mammals. *Adv. Pharmacol. Chemother.* **12**, 31-88.
- Hruska, J. (1969). DDT residues in the milk, butter, and fat of cattle. *Veterinarství* **19**, 493-498 (in Czech).
- Hsieh, H. C. (1954). DDT intoxication in a family in southern Taiwan. *Arch. Ind. Hyg. Occup. Med.* **10**, 334-346.
- Hsu, Y. N., Lin, M. T., Hong, J. S., and Tsai, M. C. (1986). Effect of chlordecone exposure on thermoregulation in the rat. *Pharmacology* **32**, 292-300.
- Huang, E. S., and Nelson, F. R. (1986). Anti-estrogenic action of chlordecone in rat pituitary gonadotrophs *in vitro*. *Toxicol. Appl. Pharmacol.* **82**, 62-69.
- Huang, Q., and Huang, X. (1987). The effect of benzene hexachloride on mouse sperm. *Zhejiang Yike Daxue Xuebao* **16**, 9-12.
- Huang, T. P., Ho, I. K., and Henendale, H. M. (1980). Assessment of neurotoxicity induced by oral administration of chlordecone (Kepone) in the mouse. *Neurotoxicology* **2**, 113-124.
- Huber, J. J. (1965). Some physiological effects of the insecticide Kepone in the laboratory mouse. *Toxicol. Appl. Pharmacol.* **7**, 516-524.
- Hudson, P. M., Yoshikawa, K., Ali, S. F., Lamb, J. C., Peel, J. R., and Hong, J. S. (1984). Estrogen-like activity of chlordecone (Kepone) on the hypothalamo-pituitary axis—effects on the pituitary enkephalin system. *Toxicol. Appl. Pharmacol.* **74**, 383-389.
- Hudson, P. M., Chen, P. H., Tilson, H. A., and Hong, J. S. (1985). Effects of *p,p'*-DDT on the rat brain concentrations of biogenic amine and amino acid neurotransmitters and their association with *p,p'*-DDT-induced tremor and hyperthermia. *J. Neurochem.* **45**, 1349-1355.
- Hueper, W. C. (1942). "Occupational Tumors and Allied Diseases." Thomas, Springfield, Illinois.
- Hundley, S. G., Hartgrove, R. W., Jr., and Webb, R. E. (1974). Transfer of endrin via milk in endrin-susceptible and resistant pine mice and the resultant effects on liver microsomal activity in the neonate. *Toxicol. Appl. Pharmacol.* **29**, 127-128.
- Hunter, C. G., and Robinson, J. (1967). Pharmacodynamics of dieldrin (HEOD). I. Ingestion by human subjects for 18 months. *Arch. Environ. Health* **15**, 614-626.
- Hunter, C. G., and Robinson, J. (1968). Aldrin, dieldrin, and man. *Food Cosmet. Toxicol.* **6**, 253-260.
- Hunter, C. G., Robinson, J., and Richardson, A. (1963). Chlorinated insecticide content in human body fat in southern England. *Br. Med. J.* **1**, 221-224.
- Hunter, C. G., Robinson, J., and Roberts, M. (1969). Pharmacodynamics of dieldrin (HEOD). Ingestion by humans subjects for 18 to 24 months and postexposure for eight months. *Arch. Environ. Health* **18**, 12-21.
- Hunter, J., Maxwell, J. D., Stewart, D. A., Williams, R., Robinson, J., and Richardson, A. (1972). Increased hepatic microsomal enzyme activity from occupational exposure to certain organochlorine pesticides. *Nature (London)* **237**, 399-401.
- Hurwitz, S. (1973). Scabies in babies. *Am. J. Dis. Child.* **126**, 226-228.
- Husejnov, M. K. (1970). The prevention of agricultural chemicals intoxication among collective farm workers. *Azerb. Med. Zh.* **47**, 27-30 (in Russian).
- Hutson, D. H. (1976). Comparative metabolism of dieldrin in two strains of mouse (FC1 and LACG). *Food Cosmet. Toxicol.* **14**, 577-591.
- Hutson, D. H., and Hoadley, E. C. (1974). The oxidation of a cyclic alcohol (12-hydroxyendrin) to a ketone (12-keto-endrin) by microsomal monooxygenation. *Chemosphere* **3**, 205-210.
- Hutter, A. M., and Kayhoe, D. E. (1966). Adrenal cortical carcinoma. II. Results of treatment with *o,p'*-DDD in 138 patients. *Am. J. Med.* **41**, 581-592.
- Hwang, E. C., and van Woert, M. H. (1978). *p,p'*-DDT-induced neurotoxic syndrome: Experimental myoclonus. *Neurology* **28**, 1020-1025.
- Iatropoulos, M. J., Milling, A., Mueller, W. F., Nohynek, G., Rozman, K., Coulston, F., and Korte, F. (1975). Absorption, transport and organotropism of dichlorobiphenyl (DCB), dieldrin, and hexachlorobenzene (HCB) in rats. *Environ. Res.* **10**, 384-389.
- Ibañez-Petersen, E. H., and DeFranzetti, R. P. (1957). Psychometric studies and their clinical value in dieldrin spraymen. *Bol. Of. Sanit. Panam.* **43**, 531-533 (in Spanish).
- Ichikawa, H. (1972). Pathology of BHC poisoning. *Biotechnol. Bioeng. Symp.* **3**, 111-116.
- Ichinose, R., and Kurihara, N. (1987). Intramolecular deuterium isotope effect and crantiotopic differentiation in oxidative demethylation of chiral (monomethyl- $d_3$ )methoxychlor in rat liver microsomes. *Biochem. Pharmacol.* **36**, 3761-3756.
- Il'yina, V. I., and Blekherman, N. A. (1974). Data on the status of the specific female functions of the organism in female workers exposed to hexachlorocyclohexane. *Pediatr., Akush. Ginekol.* **36**, 46-49 (in Russian).
- Imai, H., and Coulston, F. (1968). Ultrastructural studies of absorption of methoxychlor in the jejunal mucosa of the rat. *Toxicol. Appl. Pharmacol.* **8**, 135-158.
- Infante, P. F., Epstein, S. S., and Newton, W. A. (1978). Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. *Scand. J. Work. Environ. Health* **4**, 137-150.
- Ingle, L. (1952). Chronic oral toxicity of chlordane to rats. *Arch. Ind. Hyg. Occup. Med.* **6**, 357-367.
- Ingle, L. (1953). The toxicity of chlordane vapors. *Science* **118**, 213-214.
- Innes, J. R., Ulland, B. M., Vallerio, M. G., Petricelli, L., Fishbein, L., Hart, E. R., Pallotta, A. J., Bates, R. R., Falk, H. L., Gart, J. J., Klein, M., Mitchell, I., and Peters, J. (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. Natl. Cancer Inst. (U.S.)* **42**, 1101-1114.
- Inoue, Y., Abe, J., Takamatsu, M., and Aoki, N. (1974). A study on the qualitative and quantitative ratio of PCB and organochlorine pesticide residues in the blood and the adipose tissue. *Jpn. J. Hyg.* **29**, 92 (in Japanese).
- Interdepartmental Committee on Pest Control (1951). A statement on the health hazards of thermal generators as used for the control of flying insects. *J. Econ. Entomol.* **44**, 1027.
- Interdepartmental Committee on Pest Control (1953). A revised statement of the health hazards of insecticide vaporizers as used for the control of flying insects. *J. Econ. Entomol.* **46**, 181.
- International Agency for Research on Cancer (IARC) (1974). World Health Organization, International Agency for Research on Cancer. Some organochlorine pesticides. *IARC Monogr. Eval. Carcinog. Risk Chem. Man* **5**.
- International Agency for Research on Cancer (IARC) (1979). World Health Organization, International Agency for Research on Cancer. Some halogenated hydrocarbons. *IARC Monogr. Eval. Carcinog. Risk Chem. Man* **20**.
- International Agency for Research on Cancer (IARC) (1982). World Health Organization, International Agency for Research on Cancer. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. *IARC Monogr. Eval. Carcinog. Risk Chem. Man, Suppl.* **4**.
- International Agency for Research on Cancer (IARC) (1983). World Health Organization, International Agency for Research on Cancer. Miscellaneous Pesticides. *IARC Monogr. Eval. Carcinog. Risk Chem. Man* **30**.
- (IARC) International Agency for Research on Cancer (1987). "World Health Organization, International Agency for Research on Cancer. Overall Evaluations of Carcinogenicity: An Update of IARC Monographs 1-42," Suppl. 7. Int. Agency Res. Cancer, Lyon.
- Inuyama, Y., and Takashita, T. (1973). Survey of pesticide residues and PCB in mother's milk and human adipose tissue. *Annu. Rep. Shimane Prefect. Inst. Public Health Environ. Pollut.* **15**, 37-39 (in Japanese).
- Ireland, J. S., Mukku, V. R., Robison, A. K., and Stancel, G. M. (1980). Stimulation of uridine deoxyribonucleic acid synthesis by 1,1,1-trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane (*o,p'*-DDT). *Biochem. Pharmacol.* **29**, 1469-1474.
- Ishikawa, Y., Charalambous, P., and Matsumura, F. (1989). Modification by pyrethroids and DDT of phosphorylation activities of rat brain sodium channel. *Biochem. Pharmacol.* **38**, 2449-2457.
- Israeli, R., and Mayersdorf, A. (1973). Pathological changes in the EEG during work with halogen-containing insecticides. *Zentralbl. Arbeitsmed. Arbeitsschutz* **23**, 340-343 (in German).
- Israeli, R., Kristal, N., and Tiberin, P. (1969). Endosulfan poisoning: A preliminary report on three cases. *Zentralbl. Arbeitsmed. Arbeitsschutz* **19**, 1-3 (in German).
- Ito, K., and Umemura, N. (1973). Environmental pollution and preservation of health of mothers and their children—on the pollution by organochlorine pesticides. *Jpn. J. Public Health* **20**, 406 (in Japanese).
- Ito, K., Nagasaki, H., Arai, M., Sugihara, S., and Makiura, S. (1973). Histological and ultrastructural studies on the hepatocarcinogenicity of benzene hexachloride in mice. *JNCI, J. Natl. Cancer Inst.* **51**, 817-826.
- Ito, N., Hananouchi, M., Sugihara, S., Shirai, T., Tsuda, H., Fukushima, S., and Nagasaki, H. (1976). Reversibility and irreversibility of liver tumours in mice induced by the  $\alpha$ -isomer of 1,2,3,4,5,6-hexachlorocyclohexane. *Cancer Res.* **36**, 2227-2234.
- Ito, T., and Miyake, Y. (1973). Influence of pesticides on enzymes in living bodies. *Annu. Rep. Res. Inst. Environ. Pollut., Kinki Univ.* **1**, 5-8 (in Japanese).
- Iverson, F. (1976). Induction of paraoxon dealkylation by hexachlorobenzene (HCB) and mirex. *J. Agric. Food Chem.* **24**, 1238-1246.
- Iverson, F., Ryan, J. J., Lizotte, R., and Hierlihy, S. T. (1984). *In vivo* and *in vitro* binding of  $\alpha$ - and  $\gamma$ -hexachlorocyclohexane to mouse liver macromolecules. *Toxicol. Lett.* **20**, 331-335.
- Ivey, M. C., Claborn, H. U., Mann, H. D., Radeleff, R. D., and Woodward, G. T. (1961). Aldrin and dieldrin content of body tissues of livestock receiving aldrin in their diet. *J. Agric. Food Chem.* **9**, 374-376.
- Ivie, G. W., Gibson, J. R., Bryant, H. E., Begin, J. J., Barnett, J. R., and Dorrough, H. W. (1974). Accumulation, distribution, and excretion of mirex- $^{14}C$  in animals exposed for long periods to the insecticide in the diet. *J. Agric. Food Chem.* **22**, 646-653.
- Jacobs, P., and Lurie, J. B. (1967). Acute toxicity of the chlorinated hydrocarbon insecticides. *S. Afr. Med. J.* **41**, 1147-1150.
- Jacobziner, H., and Raybin, H. W. (1959). Briefs on accidental chemical poisonings in New York City. *N.Y. State J. Med.* **59**, 2017-2022.
- Jaeger, U., Podczek, A., Haubenstock, A., Pirich, K., Donner, A., and Hruby, K. (1984). Acute oral poisoning with lindane-solvent mixtures. *Vet. Hum. Toxicol.* **26**, 11-14.
- Jager, K. W. (1970). "Aldrin, Dieldrin, Endrin and Telodrin." Am. Elsevier, New York.
- Jager, R. J. (1976). Kepone chronology. *Science* **193**, 95-96.
- Jandacek, R. J. (1982). The effect of nonabsorbable lipids on the intestinal absorption of lipophiles. *Drug Metab. Rev.* **13**, 695-714.



- Jani, J. P., Patel, J. S., Shah, M. P., Gupta, S. K., and Kashyap, S. K. (1988). Levels of organochlorine pesticides in human milk in Ahmedabad, India. *Int. Arch. Occup. Environ. Health* **60**, 111-113.
- Jansson, B., Jensen, S., Olsson, M., Renberg, L., Sundström, G., and Vaz, R. (1975). Identification by GC-MS of phenolic metabolites of PCB and *p,p'*-DDE isolated from Baltic guillemot and seal. *Ambio* **4**, 93-97.
- Jedeikin, R., Kaplan, R., Shapira, A., Radwan, H., and Hoffman, S. (1979). The successful use of "high level" PEEP in near fatal endrin poisoning. *CRC Crit. Care Med.* **7**, 168-170.
- Jedlička, V., Heřmanská, Z., Šmida, I., and Kouba, A. (1958). Para-myeloblastic leukaemia appearing simultaneously in two blood cousins after simultaneous contact with Gammexane (hexachlorocyclohexane). *Acta Med. Scand.* **161**, 447-451.
- Jefferies, D. J., and French, M. C. (1972). Changes induced in the pigeon thyroid by *p,p'*-DDE and dieldrin. *J. Wildl. Manage.* **36**, 24-30.
- Jeffery, W. H., Ahlin, T. A., Goren, C., and Hardy, W. R. (1976). Loss of warfarin effect after occupational insecticide exposure. *JAMA, J. Am. Med. Assoc.* **236**, 2881-2882.
- Jemma, Z., Sabbah, S., Driss, M. R., and Bouguerra, M. L. (1986). Hexachlorobenzene in Tunisian mothers' milk, cord blood and foodstuffs. *IARC Publ.* **77**, 139-142.
- Jenkins, M. Q. (1964). Poisoning of the month. *J. S. C. Med. Assoc.* **60**, 17-18.
- Jenkins, R. B., and Toole, J. F. (1964). Polyneuropathy following exposure to insecticides. Two cases of polyneuropathy with albuminocytologic dissociation in the spinal fluid following exposure to DDD and aldrin and DDT and endrin. *Arch. Intern. Med.* **113**, 691-695.
- Jensen, A. A. (1983). Chemical contaminants in human milk. *Residue Rev.* **89**, 1-128.
- Jensen, G. E., and Clausen, J. (1979). Organochlorine compounds in adipose tissue of Greenlanders and southern Danes. *J. Toxicol. Environ. Health* **5**, 617-629.
- Jensen, J. A., Cueto, C., Dale, W. E., Rothe, C. F., Pearce, G. W., and Mattson, A. M. (1957). Metabolism of insecticides. DDT metabolites in feces and bile of rats. *J. Agric. Food Chem.* **5**, 919-925.
- Jensen, S., and Jansson, B. (1976). Anthropogenic substances in seal from the Baltic: Methyl sulfone metabolites of PCB and DDE. *Ambio* **5**, 257-260.
- Jeyaratnam, J., and Forshaw, J. (1974). A study of the cardiac effects of DDT in laboratory animals. *Bull. W.H.O.* **51**, 531-535.
- Johnson, B. L., and Eden, W. G. (1953). The toxicity of aldrin, dieldrin, and toxaphene to rabbits by skin absorption. *J. Econ. Entomol.* **46**, 702-703.
- Johnson, K. W., Holsapple, M. P., and Munson, A. E. (1986). An immunotoxicological evaluation of gamma-chlordane. *Fundam. Appl. Toxicol.* **6**, 317-326.
- Johnson, K. W., Kaminski, N., and Munson, A. E. (1987). Direct suppression of cultured spleen cell responses by chlordane and the basis for differential effects on *in vivo* and *in vitro* immunocompetence. *J. Toxicol. Environ. Health* **22**, 497-515.
- Jonczyk, H. (1970). The content of organochlorine insecticides in the blood of healthy persons. *Rocz. Panstw. Zakl. Hig.* **21**, 589-593 (in Polish).
- Jonsson, V., Liu, G. J. K., Armbruster, J., Kettlehut, L. L., and Drucker, B. (1977). Chlorohydrocarbon pesticide residues in human milk in Greater St. Louis, Missouri, 1977. *Am. J. Clin. Nutr.* **30**, 1106-1109.
- Jordan, J. E., Grice, T., Mishra, S. K., and Desai, D. (1981). Acute chlordecone toxicity in rats: A relationship between tremor and ATPase activities. *Neurotoxicology* **2**, 355-364.
- Joslin, E. F., Forney, R. L., Huntington, R. W., Jr., and Hayes, W. J., Jr. (1960). A fatal case of lindane poisoning. In "Proceedings of the National Association of Coroners Seminars, 1958, 1959," pp. 53-57. S. R. Gerber, Cleveland, Ohio.
- Jovčič, B., and Ivanuš, J. (1968). Variations in the electroencephalogram in workers exposed to insecticides. *Zentralbl. Arbeitsmed. Arbeitsschutz* **18**, 270-272 (in German).
- Joy, R. M. (1973). Electrical correlates of preconvulsive and convulsive doses of chlorinated hydrocarbon insecticides in the CNS. *Neuropharmacology* **12**, 63-76.
- Joy, R. M. (1974a). Alteration of sensory and motor evoked responses by dieldrin. *Neuropharmacology* **13**, 93-110.
- Joy, R. M. (1974b). Temporal sequencing of dieldrin induced epileptiform spikes in the cat. *Proc. West. Pharmacol. Soc.* **17**, 82-96.
- Joy, R. M. (1976). The alteration by dieldrin of cortical excitability conditioned by sensory stimuli. *Toxicol. Appl. Pharmacol.* **38**, 357-368.
- Joy, R. M. (1977). Contrasting actions of dieldrin and aldrin-transdiol, its metabolite, on cat CNS function. *Toxicol. Appl. Pharmacol.* **42**, 137-148.
- Joy, R. M. (1982a). Chlorinated hydrocarbon insecticides. In "Pesticides and Neurological Diseases" (D. Ecobicon and R. M. Joy, eds.), pp. 91-150. CRC Press, Boca Raton, Florida.
- Joy, R. M. (1982b). Mode of action of lindane, dieldrin and related insecticides in the central nervous system. *Neurobehav. Toxicol. Teratol.* **4**, 813-823.
- Joy, R. M. (1985). The effects of neurotoxicants on kindling and kindled seizures. *Fundam. Appl. Toxicol.* **5**, 41-65.
- Joy, R. M., and Albertson, T. E. (1985). Lindane and limbic system excitability. *Neurotoxicology* **6** (2), 193-214.
- Joy, R. M., and Albertson, T. E. (1987a). Factors responsible for increased excitability of dentate gyrus granule cells during exposure to lindane. *Neurotoxicology* **8**, 517-527.
- Joy, R. M., and Albertson, T. E. (1987b). Interactions of lindane with synaptically mediated inhibition and facilitation in the dentate gyrus. *Neurotoxicology* **8**, 529-542.
- Joy, R. M., and Albertson, T. E. (1988). Convulsant-induced changes in perforant path-dentate gyrus excitability in urethane anaesthetized rats. *J. Pharmacol. Exp. Ther.* **246**, 887-895.
- Joy, R. M., and Burns, V. W. (1988). Exposure to lindane and two other hexachlorocyclohexane isomers increases free intracellular calcium levels in neurohybridoma cells. *Neurotoxicology* **9**, 637-644.
- Joy, R. M., Stark, L. G., Peterson, S. L., Bowyer, J. F., and Albertson, T. E. (1980). The kindled seizures: Production of and modification by dieldrin in rats. *Neurobehav. Toxicol.* **2**, 117-124.
- Joy, R. M., Stark, L. G., and Albertson, T. E. (1982a). Proconvulsant effects of lindane: Enhancement of amygdaloid kindling in the rat. *Neurobehav. Toxicol. Teratol.* **4**, 347-354.
- Joy, R. M., Stark, L. G., and Schiedt, M. J. (1982b). Elevation of brain cyclic nucleotides during acute dieldrin exposure. *Bull. Environ. Contam. Toxicol.* **28**, 611-616.
- Joy, R. M., Stark, L. G., and Albertson, T. E. (1983). Proconvulsant action of lindane compared at two different kindling sites in the rat—amygdala and hippocampus. *Neurobehav. Toxicol. Teratol.* **5**, 461-465.
- Judah, J. D. (1949). Studies on the metabolism and mode of action of DDT. *Br. J. Pharmacol. Chemother.* **4**, 120-131.
- Jude, A., and Girard, P. (1949). Toxicity of DDT intoxication by accidental ingestion. *Ann. Med. Leg.* **29**, 209-213 (in French).
- Junqueira, V. B. C., Simizu, K., Videla, L. A., and Barros, S. B. DeM. (1986). Dose-dependent study of the effects of acute lindane administration on rat liver superoxide anion production, antioxidant enzyme activities and lipid peroxidation. *Toxicology* **41**, 193-204.
- Juszkiewicz, T., and Stec, J. (1971). Polychlorinated insecticide residues in adipose tissue of farmers in the Lublin Province (Poland). *Pol. Tyg. Lek.* **26**, 462 (in Polish).
- Juszkiewicz, T., Stec, J., Radomanski, T., and Trebicka-Kwiatkowska, B. (1972). Residues of chlorinated hydrocarbon insecticides in human milk. *Pol. Tyg. Lek.* **27**, 616-619 (in Polish).
- Kacew, S., and Singhal, R. L. (1972). Role of adrenals in acute effects of *p,p'*-DDT renal glucose metabolism. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **31**, 1727.
- Kacew, S., and Singhal, R. L. (1973). Adaptive response of hepatic carbohydrate metabolism to oral administration of *p,p'*-1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane in rats. *Biochem. Pharmacol.* **22**, 47-57.
- Kacew, S., Sutherland, D. J. B., and Singhal, R. L. (1973). Biochemical changes following chronic administration of heptachlor epoxide and endrin to male rats. *Environ. Physiol. Biochem.* **3**, 221-229.
- Kachole, M. S., and Pawar, S. S. (1977). Effect of endrin on microsomal electron transport reactions. Part I. Sleeping time, electron transport components and protection by pretreatment. *Indian J. Biochem. Biophys.* **14**, 45.
- Kadis, V. W., Breitkreitz, W. E., and Johansson, O. J. (1970). Insecticide levels in human tissues of Alberta residents. *Can. J. Public Health* **61**, 413-416.
- Kagan, Y. S., Rodionov, G. A., Woronina, L. Y., Velichko, L. S., Kulagin, O. M., and Peremitina, A. D. (1969). Effect of DDT on the functional and morphological condition of the liver. *Vrach. Delo* **12**, 101-105 (in Russian).
- Kailin, E. W., and Hastings, A. (1966). Electromyographic evidence of DDT-induced myasthenia. *Med. Ann. D.C.* **35**, 237-244.
- Kaku, S. (1973). An epidemiological study on organochlorine pesticide contamination. On the pesticide residues in the plasma of so-called healthy Japanese in 1971. *Kurume Igakkai Zasshi* **36**, 307-326.
- Kalra, R. L., and Chawla, R. P. (1981). Occurrence of DDT and BHC residues in human milk. *Experientia* **37**, 404-405.
- Kamata, T. (1973). On the present status of environmental pollution by organochlorine pesticide residues. *Jpn. J. Pub. Health* **20**, 405 (in Japanese).
- Kamata, T. (1974). Hygienic studies on pesticide residues. Part 4. Environmental contamination by organochlorine pesticides. *Med. J. Hiroshima Univ.* **22**, 315-325 (in Japanese).
- Kaminski, N. E., Robert, J. F., and Guthrie, F. E. (1982). The effects of DDT and dieldrin on rat peritoneal macrophages. *Pestic. Biochem. Physiol.* **17**, 191-195.
- Kaminsky, L. S., Piper, L. J., McMartin, D. N., and Fasco, M. J. (1978). Induction of microsomal cytochrome P-450 by mirex and Kepone. *Toxicol. Appl. Pharmacol.* **43**, 327-338.
- Kanitz, S., and Castello, G. (1966). On the presence of residues of some pesticides in human adipose tissue and in some foods. *G. Ig. Med. Prev.* **7**, 1-19 (in Italian).
- Kanja, L., Skare, J. U., Nafstad, I., Maitai, C. K., and Lokken, P. (1986). Organochlorine pesticide in human milk from different areas of Kenya 1983-1985. *J. Toxicol. Environ. Health* **19**, 449-464.
- Kaphalia, B. S., and Seth, T. D. (1983). Chlorinated pesticide residues in blood plasma and adipose tissue of normal and exposed human population. *Indian J. Med. Res.* **77**, 245-247.
- Kapoor, I. P., Metcalf, R. L., Nystrom, R. F., and Sangha, G. K. (1970). Comparative metabolism of methoxychlor, methiochlor, and DDT in mouse, insects, and in a model ecosystem. *J. Agric. Food Chem.* **18**, 1145-1152.
- Karakaya, A. E., and Ozalp, S. (1987). Organochlorine pesticides in human adipose tissue collected in Ankara (Turkey) 1984-1985. *Bull. Environ. Contam. Toxicol.* **38**, 941-945.
- Karakaya, A. E., Burgaz, S., and Kanzik, I. (1987). Organochlorine pesticide contaminants in human milk from different regions of Turkey. *Bull. Environ. Contam. Toxicol.* **39**, 506-510.
- Karapally, J. C., Saha, J. G., and Lee, Y. W. (1973). Metabolism of lindane-<sup>14</sup>C in the rabbit: Ether soluble urinary metabolites. *J. Agric. Food Chem.* **21**, 811-818.
- Karimov, A. M. (1969). Skin sensitivity to organochlorine insecticides. *Med. Zh. Uzb.* **9**, 58-60 (in Russian).
- Karimov, A. M. (1970). Occupational skin diseases in cotton growers caused by chemical poisons and measures for their prevention. *Gig. Tr. Prof. Zabol.* **14**, 35-37 (in Russian).
- Karnik, A. B., Thakore, K. N., Nigam, S. K., Babu, K. A., Lakkad, B. C., Bhatt, D. K., Kashyap, S. K., and Chatterjee, S. K. (1981). Studies on glucose-6-phosphatase, fructose-1,6-diphosphatase activity, glycogen and endoplasmic reticulum changes during hexachlorocyclohexane induced hepatocarcinogenesis in pure inbred Swiss mice. *Neoplasma* **28**, 575-584.
- Karplus, M. (1971). Endrin poisoning in children. *Harefuah* **81**, 113-116 (in Hebrew).
- Kasai, A., Asanuma, S., and Nakamura, S. (1972). Studies on organochlorine pesticide residues in human organs. Part II. *J. Jpn. Assoc. Rural Med.* **21**, 296-297 (in Japanese).
- Kashyap, S. K. (1986). Health surveillance and biological monitoring of pesticide formulators in India. *Toxicol. Lett.* **33**, 107-114.
- Kashyap, S. K., Nigam, S. K., Karnik, A. B., Gupta, R. C., and Chatterjee, S. K. (1977). Carcinogenicity of DDT (dichlorodiphenyltrichloroethane) in pure inbred Swiss mice. *Int. J. Cancer* **19**, 725-729.
- Kashyap, S. K., Nigam, S. K., Gupta, R. C., Karnik, A. B., and Chatterjee, S. K. (1979). Carcinogenicity of hexachlorocyclohexane (BHC) in pure inbred Swiss mice. *J. Environ. Sci. Health, Part B* **14**, 305-318.
- Kashyap, S. K., Gupta, S. K., Karnik, A. B., Parikh, J. R., and Chatterjee, S. K. (1980). Scope and need of toxicological evaluation of pesticides under field conditions—medical surveillance of malaria spraymen exposed to HCH (hexachlorocyclohexane) in India. *Stud. Environ. Sci.* **7**, 53-61.
- Kato, K., Yamada, T., Watanabe, S., Wada, Y., Fukuda, M., Kuroda, M., Nakaoka, S., Takahashi, T., Miyashiro, K., Masuda, J., and Yasukata, S. (1971). Analyses of residual pesticides in vegetables, cows' milk and mothers' milk. *Annu. Rep. Kanazawa Prefect. Inst. Public Health* **21**, 85-92 (in Japanese).
- Katsenovich, R. A., and Usmanova, I. Y. (1970). On the appearance of liver autoantibodies in persons in contact with pesticides. *Med. Zh. Uzb.* **7**, 6-8 (in Russian).
- Kauer, K., DuVall, R., and Alquist, F. (1947). Epsilon isomer of 1,2,3,4,5,6-hexachlorocyclohexane. *Ind. Eng. Chem.* **39**, 1335-1338.
- Kaul, R., Klein, W., and Korte, F. (1970). Contributions to ecological chemistry. XX. Distribution, excretion and metabolism of Telodrin and heptachlor in rats and male rabbits. The end product of heptachlor metabolism in warm-blooded animals. *Tetrahedron* **26**, 331-337.
- Kavlock, R. J., Chernoff, N., Rogers, E., and Whitehouse, D. (1980). Comparative tissue distribution of mirex and chlordecone in fetal and neonatal rats. *Pestic. Biochem. Physiol.* **14**, 227-235.
- Kavlock, R. J., Chernoff, N., Hanisch, R. C., Gray, J., Rogers, E., and Gray, L. E. (1981). Perinatal toxicity of endrin in rodents. II. Fetotoxic effects of prenatal exposure in rats and mice. *Toxicology* **21**, 141-150.
- Kawahara, T., and Moku, M. (1972). Studies on organochlorine pesticide residues in crops and soils. Report XVI. Degradation and isomerization of BHC isomers by heating. *Bull. Agric. Chem. Insp. Stn. (Jpn.)* **12**, 35-37.
- Kawai, Y., Hori, Y., Nigawa, Y., Yamamoto, I., Tsuzuki, T., Kitayama, M., and Mori, K. (1973). On the pollution of mothers' milk by pesticides and PCB in Hokkaido. *J. Food Hyg. Soc. Jpn.* **14**, 302-303 (in Japanese).
- Kawanishi, A., Asanuma, S., and Nakamura, S. (1973). Studies on the organochlorine pesticide residues in humans. Report 4. *J. Jpn. Assoc. Rural Med.* **22**, 278-279 (in Japanese).
- Kawano, M., and Tatsukawa, R. (1982). Chlordanes and related compounds in blood of pest control operators (PCOs). *Nippon Nogei Kagaku Kaishi* **56**, 923-929 (in Japanese).
- Kay, R. W. W., Kuder, G. G., Sessler, W. A., and Lewis, R. (1964). Fatal poisoning from ingestion of benzene hexachloride. *Ghana Med. J.* **3**, 72-74.
- Kazakevich, R. L. (1974). State of the nervous system in persons with a prolonged professional contact with hexachlorocyclohexane and products of its synthesis. *Vrach. Delo* **2**, 129-133 (in Russian).
- Kazantzis, G., McLaughlin, A. I. G., and Prior, P. F. (1964). Poisoning in industrial workers by the insecticide aldrin. *Br. J. Ind. Med.* **21**, 46-51.
- Kazen, C., Bloomer, A., Welch, R., Oudbier, A., and Price, H. (1974). Persistence of pesticides on the hands of some occupationally exposed people. *Arch. Environ. Health* **29**, 315-318.
- Keane, W. T., and Zvon, M. R. (1969a). The total body burden of dieldrin. *Bull. Environ. Contam. Toxicol.* **4**, 1-16.
- Keane, W. T., and Zvon, M. R. (1969b). Dieldrin poisoning in dogs: Relation to obesity and treatment. *Br. J. Ind. Med.* **26**, 338-341.
- Keames, C. W., Weinman, C. G., and Decker, G. C. (1949). Insecticidal properties of some new chlorinated organic compounds. *J. Econ. Entomol.* **42**, 127-134.
- Keil, J. E., Weston, W., III, Loadholt, C. B., Sandifer, S. H., and Colcough, J. J. (1972a). DDT and DDE residues in blood from children, South Carolina—1970. *Pestic. Monit. J.* **6**, 1-3.
- Keil, J. E., Sandifer, S. H., Finklea, J. H., and Priester, L. E. (1972b). Serum vitamin A elevation in DDT exposed volunteers. *Bull. Environ. Contam. Toxicol.* **8**, 317-320.
- Keil, J. E., Loadholt, C. B., Sandifer, S. H., Weston, W., III, Gadsden, R.



- H., and Hames, C. G. (1973). Sera DDT elevation in black components of two southeastern communities: Genetics or environment? In "Pesticides and the Environment: A Continuing Controversy" (W. B. Diechman ed.), pp. 203-213. Intercontinental Medical Book Corp., New York.
- Keller, W. C., and Yeary, R. A. (1980). A comparison of the effects of mineral oil, vegetable oil and sodium sulfate on the intestinal absorption of DDT in rodents. *Clin. Toxicol.* **16**, 223-231.
- Kelner, M. J., McLenithan, J. C., and Anders, M. W. (1986). Thiol stimulation of the cytochrome P-450-dependent reduction of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) to 1,1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDD). *Biochem. Pharmacol.* **35**, 1805-1807.
- Kelvay, L. M. (1970). Endrin excretion by the isolated perfused liver: A sexual difference. *Proc. Soc. Exp. Biol. Med.* **136**, 878-879.
- Kendall, M. W. (1974a). Acute histopathologic alterations induced in livers of rat, mouse, and quail by the fire-ant poison, mirex. *Anat. Rec.* **178**, 388.
- Kendall, M. W. (1974b). Acute hepatotoxic effects of mirex in the rat. *Bull. Environ. Contam. Toxicol.* **12**, 617-621.
- Kendall, M. W. (1979). Light and electron microscopic observations of the acute sublethal hepatotoxic effects of mirex in the rat. *Arch. Environ. Contam. Toxicol.* **8**, 25-41.
- Kennedy, G. L., Jr., Frawley, J. P., and Calendra, J. C. (1973). Multigeneration reproductive effects of three pesticides in rats. *Toxicol. Appl. Pharmacol.* **25**, 589-596.
- Kennedy, M. W., Pittman, K. A., and Stein, V. M. (1975). Fate of  $^{14}\text{C}$  mirex in the female rhesus monkey. *Toxicol. Appl. Pharmacol.* **33**, 161-162.
- Keplinger, M. L. (1963). Use of humans to evaluate safety of chemicals. *Arch. Environ. Health* **6**, 342-349.
- Keplinger, M. L., and Diechmann, W. B. (1968). Susceptibility of offspring of mice fed pesticides to single oral doses of pesticides. *Am. Ind. Hyg. Assoc. J.* **29**, Suppl. 2, 111-112.
- Keplinger, M. L., Diechmann, W. B., and Sala, F. (1970). Effect of combinations of pesticides on reproduction in mice. In "Pesticides Symposia" (W. B. Diechmann, J. L. Radomski, and R. A. Penalver, eds.), pp. 125-138. Halos and Associates, Miami, Florida.
- Khaikina, B. I., and Shilina, V. F. (1971). The effect on serotonin metabolism of some organochlorine pesticides. *Farmakol. Toksikol. (Moscow)* **34**, 357-359 (in Russian).
- Khaikina, B. I., Kuz'minskaia, U. A., and Alakhina, S. M. (1970). The effect of some pesticides on the isoenzymatic activity of serum lactic dehydrogenase. *Byull. Eksp. Biol. Med.* **70**, 39-41 (in Russian).
- Khairi, M. (1959). Changes in behaviour associated with a nervous system poison (DDT). *Q. J. Exp. Physiol.* **11**, 91-94.
- Khalifa, S., Mon, T. R., Engel, J. L., and Casida, J. E. (1974). Isolation of 2,2,5-endo,6-exo,3,9,10-heptachlorobornane and an octachloro toxicant from technical toxaphene. *J. Agric. Food Chem.* **22**, 653-657.
- Khalifa, S., Holmstead, R. L., and Casida, J. E. (1976). Toxaphene degradation by iron(II) protoporphyrin system. *J. Agric. Food Chem.* **24**, 277-282.
- Khanna, R. N., Misra, D., Anand, M., and Sharma, H. K. (1979). Distribution of endosulfan in cat brain. *Bull. Environ. Contam. Toxicol.* **22**, 72-79.
- Khare, S. B., Rizvi, A. G., Shukla, O. P., Singh, R. R. P., Perkash, O., Misra, V. D., Gupta, J. P., and Sethi, P. K. (1977). Epidemic outbreak of neuro-ocular manifestations due to chronic BHC poisoning. *J. Assoc. Physicians India* **25**, 215-222.
- Khasawinah, A. M., and Grutsch, J. F. (1989a). Chlordane: thirty-month tumorigenicity and chronic toxicity test in rats. *Reg. Toxicol. Pharmacol.* **10**, 95-109.
- Khasawinah, A. M., and Grutsch, J. F. (1989b). Chlordane: a 24-month tumorigenicity and chronic test in mice. *Regul. Toxicol. Pharmacol.* **10**, 244-254.
- Khasawinah, A. M., Hardy, C. J., and Clark, G. C. (1989). Comparative inhalation toxicity of technical chlordane in rats and monkeys. *J. Toxicol. Environ. Health* **28**, 327-347.
- Khera, K. S., Villeneuve, D. C., Terry, G., Panopio, L., Nash, L., and Trivett, G. (1976). Mirex: A teratogenicity, dominant lethal and tissue distribution study in rats. *Food Cosmet. Toxicol.* **14**, 25-29.
- Khera, K. S., Whalen, C., and Trivett, G. (1978). Teratogenicity studies on linuron, malathion, and methoxychlor in rats. *Toxicol. Appl. Pharmacol.* **45**, 435-444.
- Khomenko, N. R., and Kazakevich, R. L. (1973). Abnormalities of the knee reflex in chronic BHC and thiram poisoning. *Gig. Tr. Prof. Zabol.* **17**, 56-57 (in Russian).
- Kim, A. S., Aminov, K. A., and Zaitsev, A. A. (1967). Psychosis with poisoning by fenthion and hexachlorane. *Nauchn. Tr., Samark. Med. Inst.* **37**, 282-287 (in Russian).
- Kimbrough, R. D., Gaines, T. B., and Hayes, W. J., Jr. (1968). Combined effect of DDT, pyrethrum, and piperonyl butoxide on rat liver. *Arch. Environ. Health* **16**, 333-341.
- Kinoshita, F. K., and Kempf, C. K. (1970). Quantitative measurements of hepatic microsomal enzyme induction after dietary intake of chlorinated hydrocarbon insecticides. *Toxicol. Appl. Pharmacol.* **17**, 288.
- Kinoshita, F. K., Frawley, J. P., and DuBois, K. P. (1966). Quantitative measurement of induction of hepatic microsomal enzymes by various dietary levels of DDT and toxaphene in rats. *Toxicol. Appl. Pharmacol.* **9**, 505-513.
- Kitselman, C. H. (1953). Long term studies on dogs fed aldrin and dieldrin in sublethal dosages, with references to the histopathological findings and reproduction. *J. Am. Vet. Med. Assoc.* **123**, 28.
- Klayman, M. B. (1968). Exposure to insecticides. *Arch. Otolaryngol.* **88**, 116-117.
- Klein, A. K., Laug, E. P., Datta, P. R., and Mendel, J. L. (1965). Evidence for the conversion of  $o,p'$ -DDT (1,1,1-trichloro-2- $o$ -chlorophenyl-2- $p$ -chlorophenylethane) to  $p,p'$ -DDT (1,1,1-trichloro-2,2-bis( $p$ -chlorophenyl)ethane) in rats. *J. Am. Chem. Soc.* **87**, 2520-2522.
- Klein, A. K., Laug, E. P., Datta, P. R., Watts, J. O., and Chen, J. T. (1969a). Metabolites: Reductive dechlorination of DDT to DDD and isomeric transformation of  $o,p'$ -DDT to  $p,p'$ -DDD in vitro. *J. Assoc. Off. Anal. Chem.* **47**, 1129-1145.
- Klein, A. K., Kaul, R., Parlar, Z., Zimmer, M., and Korte, F. (1969b). Contributions to ecological chemistry. XIX. Metabolism of photodieldrin-14-C in warm-blooded animals, insects, and plants. *Tetrahedron Lett.*, pp. 3197-3199.
- Klein, A. K., Dailey, R. E., Walton, M. S., Beck, V., and Link, J. D. (1970). Metabolites isolated from urine of rats fed  $^{14}\text{C}$ -photodieldrin. *J. Agric. Food Chem.* **18**, 705-708.
- Klein, W., and Korte, F. (1970). Metabolism of chlorinated hydrocarbons. In "Chemistry of Plant Protection and Pest Control Agents" (R. Wegler, ed.), Vol. 1, pp. 199-218. Springer-Verlag, Berlin (in German).
- Klein, W., Mueller, W., and Korte, F. (1968). Insecticides in metabolism. 16. Excretion, distribution and metabolism of C-14 endrin rats. *Ann. Chim. (Paris)* **7**, [13], 180-185.
- Kleine-Natrop, H. E., Roder, H., and Kadner, H. (1970). Note on timely scabies treatment. *Dtsch. Gesundheitswes.* **25**, 2082-2084 (in German).
- Kleinfeld, M. (1967). Cancer of urinary bladder in a dye plant: A medical environmental study. In: "Bladder Cancer: A Symposium" (W. B. Diechmann, ed.), Aesculapius, Birmingham, Alabama.
- Kleissner, M., and Worden, A. N. (1959). BHC and bone marrow. *Br. Med. J.* **1**, 971.
- Klevay, L. M. (1970). Dieldrin excretion by the isolated perfused rat liver: A sexual difference. *Toxicol. Appl. Pharmacol.* **17**, 813-815.
- Klimmer, O. R. (1955). Experimental investigations of the toxicology of chlorinated hydrocarbon insecticides. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **227**, 183-195 (in German).
- Klingensmith, J. S., and Mehendale, H. M. (1982). Chlordecone-induced fat depletion in the male rat. *J. Toxicol. Environ. Health* **10**, 121-129.
- Klingensmith, J. S., and Mehendale, H. M. (1983a). Hepatic microsomal metabolism of  $\text{CCl}_4$  after pretreatment with chlordecone, mirex or phenobarbital in male rats. *Drug Metab. Dispos.* **11**, 329-334.
- Klingensmith, J. S., and Mehendale, H. M. (1983b). Destruction of hepatic mixed-function oxygenase parameters by  $\text{CCl}_4$  in rats following acute treatment with chlordecone, mirex and phenobarbital. *Life Sci.* **33**, 2339-2348.
- Klinger, W., Gmyrek, D., and Gruebner, I. (1973). Investigation of different substances and classes of substances. III. Chlorinated insecticides. *Arch. Int. Pharmacodyn. Ther.* **202**, 270-280 (in German).
- Klossa, J. (1950). On the toxicology of hexachlorocyclohexane. *Pharmazie* **5**, 615-616 (in German).
- Klotz, H. P., Thibaut, E., and Russo, F. (1971). Weak doses of  $o,p'$ -DDD in the spanomenorrhea with hypertrichosis. *Ann. Endocrinol.* **32**, 763-767 (in French).
- Kluge, W., and Olbrich, H. (1972). Poisoning by a DDT-lindane combination. *Z. Aerzt. Fortbild.* **66**, 980-982 (in German).
- Knoll, W., and Jayaraman, S. (1972a). Organochlorine pesticide residues in human milk. *Z. Gesamte Hyg. Ihre Grenzgeb.* **19**, 43-45 (in German).
- Knoll, W., and Jayaraman, S. (1972b). On the contamination of human milk with chlorinated hydrocarbons. *Nahrung* **17**, 599-615 (in German).
- Knoll, W., and Jayaraman, S. (1973). Organochlorine pesticide residues in human milk. *Z. Gesamte Hyg. Ihre Grenzgeb.* **19**, 43-45 (in German).
- Knoll, W., and Jayaraman, S. (1973). On the contamination of human milk with chlorinated hydrocarbons. *Nahrung* **17**, 599-615 (in German).
- Knowles, C. O., and Ahmad, S. (1971). Comparative metabolism of chlorobenzilate, chloropropylate and bromopropylate acaricides by rat hepatic enzymes. *Can. J. Physiol. Pharmacol.* **49**, 590-597.
- Koch, R. B. (1969). Chlorinated hydrocarbon insecticides. Inhibition of rabbit brain ATPase activities. *J. Neurochem.* **16**, 269-271.
- Koch, R. B., Patel, T. N., Glick, B., Stinson, R. J., and Lewis, E. A. (1979). Properties of an antibody to kelevan isolated by affinity chromatography: Antibody reactivation of ATPase activities inhibited by pesticides. *Pestic. Biochem. Physiol.* **12**, 130-140.
- Kodavanti, P. R. S., Joshi, U. M., Young, R. A., Bell, A. N., and Mehendale, H. M. (1989). Role of hepatocellular regeneration in chlordecone potentiated hepatotoxicity of carbon tetrachloride. *Arch. Toxicol.* **63**, 367-375.
- Kohli, K. K., Chandrasekaran, V. P., and Venkatasubramanian, T. A. (1977). Stimulation of serotonin metabolism by dieldrin. *J. Neurochem.* **28**, 1397-1399.
- Kojima, S., Saito, M., Konno, H., and Ozawa, K. (1971). Results of investigation of organochlorine pesticide residues in mothers' milk and in the blood of the mothers. *Annu. Rep. Akita Prefect. Inst. Public Health* **16**, 65-68 (in Japanese).
- Kolmodin, B., Azarnoff, D. L., and Sjöqvist, F. (1969). Effect of environmental factors on drug metabolism: Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. *Clin. Pharmacol. Ther.* **10**, 638-642.
- Kolmodin-Hedman, B. (1973a). Decreased plasma half-life of phenylbutazone in workers exposed to chlorinated pesticides. *Eur. J. Clin. Pharmacol.* **5**, 195-198.
- Kolmodin-Hedman, B. (1973b). Changes in drug metabolism and lipoproteins in workers occupationally exposed to DDT and lindane. *Arch. Hig. Rada Toksikol.* **24**, 289-296.
- Kolmodin-Hedman, B., Alexanderson, B., and Sjöqvist, F. (1971). Effect of exposure to lindane on drug metabolism. Decreased hexobarbital sleeping times and increased antipyrine disappearance rate in rats. *Toxicol. Appl. Pharmacol.* **20**, 299-307.
- Kolyada, I. S., and Mikhail'chenkova, O. F. (1973). Acute organochlorine pesticide poisoning. *Gig. Tr. Prof. Zabol.* **17**, 43 (in Russian).
- Komarova, L. I. (1970). The excretion of DDT in mothers' milk and its effect on the organism of mother and child. *Pediatr., Akush. Ginekol.* **1**, 19-20 (in Russian).
- Komissarenko, V. P., and Reznikov, A. G. (1970). Chlodithane ( $o,p'$ -DDD) treatment in Itsenko-Cushing's disease. *Vrach. Delo* **8**, 107-112 (in Russian).
- Komissarenko, V. P., Reznikov, A. G., Gordienko, V. M., and Zak, K. P. (1968). Effect of  $o,p'$ -DDD on the morphology and function of adrenal cortex in dogs. *Endocrinol. Exp.* **2**, 21-28 (in Russian).
- Komissarenko, V. P., Reznikov, A. G., and Gordienko, V. M. (1970). An experimental study of the action of  $o,p'$ -DDD on the functioning and structure of the adrenal cortex. *Vopr. Endocrinol. Obmena Veschestv. Sb.* **1**, 5-10 (in Russian).
- Komissarenko, V. P., Karvchenko, V. O., Tron'ko, M. D., and Turchin, I. S. (1971). Effect of  $o,p'$ -DDD (clodithane) on secretion and metabolism of corticosteroids in chickens. *Fiziol. Zh. (Kiev, 1955-1957)* **17**, 435-441 (in Russian).
- Komissarenko, V. P., Gordiyenko, V. M., and Reznikov, A. G. (1972). Restorative processes in the adrenal cortex of dogs following administration of TDE. *Probl. Endocrinol.* **18**, 74-81 (in Russian).
- Komissarenko, V. P., Chelnakova, I. S., and Mikosha, A. S. (1978). The activity of glutathione reductase in the adrenal glands and the liver of dogs following the administration of  $o,p'$ -DDD, Perthane and ACTH. *Probl. Endocrinol.* **24**, 95-98 (in Russian).
- Komulainen, H., and Bondy, S. C. (1987). Modulation of levels of free calcium within synaptosomes by organochlorine insecticides. *J. Pharmacol. Exp. Ther.* **241**, 575-581.
- Konat, G., and Clausen, J. (1973). The cytochrome P-450 complex and esterase of the liver and brain in lindane, Aroclor 1254, and DDT-induced intoxication of the mouse. *Environ. Physiol. Biochem.* **3**, 139-147.
- Kontek, M., Kubacki, S., Paradowski, S., and Wierzchowiecka, B. (1971). Chlorinated insecticides in human milk. *Pediatr. Pol.* **46**, 183-188.
- Kontek, M., Banaszak, S., Didowicz-Parzycka, J., Kubacki, S., and Kossowski, A. (1981). Comparative investigations of organic chloride pesticides in human milk before and after withdrawal of these agents from chemical plant protection. *Pol. Tyg. Lek.* **36**, 9-11 (in Polish).
- Koransky, W., and Ullberg, S. (1964). Distribution in the brain of  $^{14}\text{C}$ -benzenehexachloride. Autoradiographic study. *Biochem. Pharmacol.* **13**, 1537-1538 (plus plates).
- Koransky, W., Portig, J., and Münch, G. (1963). Absorption, distribution and metabolism of  $\alpha$ - and  $\gamma$ -hexachlorocyclohexane. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **244**, 564-575 (in German).
- Koransky, W., Magour, S., Noack, G., and Schulte Hermann, R. (1969). The influence of inducing substances on drug-oxidases and other redox enzymes of the liver. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **263**, 281-296 (in German).
- Koransky, W., Münch, G., Noack, G., Portig, J., Sodomann, S., and Wirsching, M. (1975). Biodegradation of  $\alpha$ -hexachlorocyclohexane. V. Characterization of the major urinary metabolites. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **288**, 65-78 (in German).
- Korpachev, V. U. (1972a). Dependence of  $o,p'$ -DDD absorption on dose and drug form. *Farm Zh.* **27**, 64-66 (in Russian).
- Korpachev, V. U. (1972b). Accumulation and elimination of  $o,p'$ -DDD in organs and tissues of guinea pigs and dogs. *Fiziol. Zh.* **18**, 585-590 (in Russian).
- Korte, F. (1979). Transformation of  $p,p'$ -DDT in the environment. In "Environmental Health Criteria 9. DDT and Its Derivatives." United Nations Environmental Programme and the World Health Organization, Geneva.
- Korte, F., and Kochen, W. (1966). Metabolism of insecticides. XII. Isolation and identification of metabolites of  $^{14}\text{C}$  aldrin from the urine of rabbit. *Med. Pharmacol. Exp.* **15**, 409-414 (in German).
- Korth-Schutz, S., Levine, L. S., Roth, J. A., Saenger, P., and New, M. I. (1977). Virilizing adrenal tumor in a child suppressed with dexamethasone for three years. Effect of  $o,p'$ -DDD on serum and urinary androgens. *J. Clin. Endocrinol. Metab.* **44**, 433-439.
- Koschier, F. J., Gigliotti, P. J., and Hong, S. K. (1980). The effect of bis( $p$ -chlorophenyl)acetic acid on the renal function of the rat. *J. Environ. Pathol. Toxicol.* **4**, 209-217.
- Koster, R. (1947). Differentiation of gluconate, glucose, calcium, insulin effect on DDT poisoning in cats. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **6**, 346.
- Kostiuk, O. T., and Mukhtarova, N. D. (1970). Catecholamines and the functional state of the hypothalamus under the action of a complex of organochlorine and organophosphorus pesticides. *Gig. Tr. Prof. Zabol.* **14**, 35-38 (in Russian).
- Kotlarek-Haus, S., Dzierzkowa-Borodej, W., and Lawinska, B. (1971). Auto-immune hemolytic anemia after handling insecticides and herbicides, with simultaneous detection of the Australia antigen (Au 1) in the serum. *Folia Haematol. (Leipzig)* **95**, 249-253 (in German).
- Kramer, M. S., Hutchinson, T. A., Rudnick, S. A., Leventhal, J. M., and Feinstein, A. R. (1980). Operational criteria for adverse drug reactions in



- evaluating suspected toxicity of a popular scabicide. *Clin. Pharmacol. Ther.* **27**, 149-155.
- Krampl, V., and Grigel, M. (1972). Relationships between serum enzymes and morphological changes occurring in the rat liver after administration of and morphological changes occurring in the rat liver after administration of chlorinated cyclodiene insecticides. *Prak. Lek.* **24**, 121-125 (in Czech).
- Krampl, V., and Hladka, A. (1974). The effect of simultaneous administration of lindane and phenobarbital upon stimulation of microsomal liver enzymes. *Prak. Lek.* **26**, 169-172 (in Czech).
- Krampl, V., and Hladka, A. (1975). Dose-dependent extent of microsomal enzyme induction by aldrin and dieldrin in rats. *Bull. Environ. Contam. Toxicol.* **14**, 571-578.
- Krasil'shchikov, D. G. (1972). The penetration of hexachlorane into white rat liver and adipose tissue as affected by the presence of determents in water. *Gig. Sanit.* **37**, 96-97.
- Krasnyuk, E. P. (1964a). Electrocardiographic changes in persons working with organic chlorine insecticides. *Sov. Med.* **28**, 134-137 (in Russian).
- Krasnyuk, E. P. (1964b). The internal secretory function in persons working with organochlorine insecticides. In "Labor Hygiene," pp. 186-190. Zdorov'ya, Kiev (in Russian).
- Krasnyuk, E. P. (1969). Ballistocardiographic changes in those working with organochlorine compounds. *Gig. Tr.* **5** (1), 203-207 (in Russian).
- Krasnyuk, E. P., and Platonova, V. I. (1969). Functional disorders of the stomach under the prolonged effects of organochlorine chemical poisons. *Vrach. Delo.* **9**, 99-101 (in Russian).
- Krasnyuk, E. P., Onikiyenko, F. A., and Osknskaya, L. S. (1967). Pathology of the liver in persons working with DDT. *Vrach. Delo* **1**, 92-95 (in Russian).
- Krasnyuk, E. P., Loganovskii, N. G., Makovskaya, E. I., and Rappoport, M. B. (1968). Functional and morphological changes in the kidneys during the effects of DDT on the body. *Sov. Med.* **31**, 38-42 (in Russian).
- Kraus, P., Noack, G., and Portig, J. (1973). Biodegradation of alpha-hexachlorocyclohexane. II. Glutathione-mediated conversion to hydrophilic substance by particulate fractions of rat liver and by homogenates of various rat organs. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **279**, 199-202 (in German).
- Kraus, P., Gross, B., and Kloft, H. D. (1981). The elevation of rat liver glutathione-S-transferase activity by alpha-hexachlorocyclohexane. *Biochem. Pharmacol.* **30**, 355-361.
- Krauthacker, B., Alebic-Kolbah, T., Buntic, A., Tkalčević, B., and Reiner, E. (1980a). Organochlorine pesticides in blood serum of the general Yugoslav population and in occupationally exposed workers. *Int. Arch. Occup. Environ. Health* **45**, 217-220.
- Krauthacker, B., Alebic-Kolbah, T., Kralj, M., Tkalčević, B., and Reiner, E. (1980b). DDT residues in samples of human milk, and in mothers' and cord blood serum in a continental town in Croatia (Yugoslavia). *Int. Arch. Occup. Environ. Health* **46**, 267-273.
- Krauthacker, B., Kralj, M., Tkalčević, B., and Reiner, E. (1986). Levels of  $\beta$ -HCH, HCB,  $p,p'$ -DDE,  $p,p'$ -DDT and PCBs in human milk from a continental town in Croatia, Yugoslavia. *Int. Arch. Occup. Environ. Health* **58**, 69-74.
- Kravchenko, V. I. (1973). The effect of  $o,p'$ -DDD on the formulation of corticosteroids by the adrenal tissue *in vitro*. *Probl. Endokrinol.* **19**, 76-79 (in Russian).
- Kravt'sova, O. L., Korenevs'ky, L. I., and Reznikov, O. H. (1971). The influence of  $o,p'$ -DDD on the development of DMBA-induced mammary gland tumors and adrenal cortex function in rats. *Dopov. Akad. Nauk. Ukr. RSR, Ser. B: Geol., Geofiz., Khim. Biol.* **30** (3), 943-945 (in Russian).
- Kreiss, K., Zack, M. M., Kimbrough, R. D., and Needham, L. C. (1981). Cross-sectional study of a community with exceptional exposure to DDT. *JAMA, J. Am. Med. Assoc.* **245**, 1926-1930.
- Krijnen, C. J., and Boyd, E. M. (1971). The influence of diets containing from 0 to 81 per cent of protein on tolerated doses of pesticides. *Comp. Gen. Pharmacol.* **2**, 373-376.
- Kroger, M. (1972). Insecticide residues in human milk. *J. Pediatr.* **80**, 401-405.
- Krzystyniak, K., Hugo, P., Flipo, D., and Fournier, M. (1985). Increased susceptibility to mouse hepatitis virus 3 of peritoneal macrophages exposed to dieldrin. *Toxicol. Appl. Pharmacol.* **80**, 397-408.
- Krzystyniak, K., Bernier, J., Hugo, P., and Fournier, M. (1986). Suppression of MHV3 virus-activated macrophages by dieldrin. *Biochem. Pharmacol.* **35**, 2577-2586.
- Kuebrich, W., and Urban, I. (1973). Endrin poisoning—a contribution to the neurophysiology of epileptic attacks. *Z. Aertl. Fortbild.* **67**, 1076-1078.
- Kujawa, M., Macholz, R., and Knoll, R. (1985). Enzymic degradation of DDT. Part 5. Direct transformation of DDD (dichlorodiphenyldichloroethane) to an aldehyde. *Nahrung* **29**, 517-522.
- Kumar, A., and Dwivedi, P. O. (1988). Relative induction of molecular forms of cytochrome P-450 in  $\gamma$ -hexachlorocyclohexane exposed rat liver microsomes. *Arch. Toxicol.* **62**, 479-481.
- Kundiev, Yu. I., and Krasnyuk, E. P. (1965). Possible consequences of the introduction of hexachloran into the soil. *Hyg. Sanit. (USSR)* **30**, 116-119 (in Russian).
- Kunz, W., Schaud, G., Schmid, W., and Siess, M. (1966). Liver hypertrophy caused by foreign agents. *Naunyn-Schmiedeberg's Arch. Pharmacol. Exp. Pathol.* **254**, 470-488 (in German).
- Kunze, F. M., Laug, E. P., and Prickett, C. S. (1950). The storage of methoxychlor in the fat of the rat. *Proc. Soc. Exp. Biol. Med.* **75**, 415-416.
- Kupfer, D. (1967). Effects of some pesticides and related compounds on steroid function and metabolism. *Residue Rev.* **19**, 11-30.
- Kupfer, D., and Bulger, W. H. (1979). A novel *in vitro* method for demonstrating proestrogens. Metabolism of methoxychlor and  $o,p'$ -DDT by liver microsomes in the presence of uteri and effects on intracellular distribution of estrogen receptors. *Life Sci.* **25**, 975-984.
- Kupfer, D., and Bulger, W. H. (1987). Biochemical toxicology of methoxychlor and related chlorinated hydrocarbons. *Rev. Biochem. Toxicol.* **8**, 183-215.
- Kupfer, D., Bulger, W. H., and Nanni, F. (1986). Characteristics of the active oxygen in covalent binding of the pesticide methoxychlor to hepatic microsomal proteins. *Biochem. Pharmacol.* **35**, 2775-2780.
- Kurihara, N., and Nakajima, M. (1974). Studies on BHC isomers and related compounds. VIII. Urinary metabolites produced from  $\gamma$ - and  $\beta$ -BHC in the mouse: Chlorophenyl conjugates. *Pestic. Biochem. Physiol.* **4**, 220-231.
- Kurihara, N., Tanaka, K., and Nakajima, M. (1979). Mercapturic acid formation from lindane in rats. *Pestic. Biochem. Physiol.* **10**, 137-150.
- Kuroda, H., Yano, T., Kagawa, K., and Mitsumune, M. (1972). On the residual organochlorine pesticides in mothers' milk. *J. Shikoku Public Health Soc.* **17**, 79-80 (in Japanese).
- Kürsat, A., and Türkoğlu, N. (1968). Interesting poisoning cases with dieldrin and other insecticides. *Saglik Derg.* **42**, 3-20 (in Turkish).
- Kurt, T. L., Bost, R., Gilliland, M., Reed, G., and Petty, C. (1986). Accidental Kwell (lindane) ingestions. *Vet. Hum. Toxicol.* **28**, 569-571. Note: the wrong title and authors were printed in the original. See *Index Medicus* Vol. 28.
- Kutz, F. W., Yobs, A. R., Johnson, W. G., and Wiersma, G. B. (1974a). Mirex residues in human adipose tissue. *Environ. Entomol.* **3**, 882-884.
- Kutz, F. W., Yobs, A. R., Johnson, W. G., and Wiersma, G. B. (1974b). Pesticide residues in adipose tissue of the general population of the United States, FY 1970 survey. *Bull. Soc. Pharmacol. Environ. Pathol.* **2**, 4-10.
- Kutz, F. W., Sovocool, W., Strassman, S., and Lewis, R. G. (1976). trans-Nonachlor residues in human adipose tissue. *Bull. Environ. Contam. Toxicol.* **16**, 9-14.
- Kutz, F. W., Yobs, A. R., Strassman, S. C., and Viar, J. F., Jr. (1977). Effects of reducing DDT usage on total DDT storage in humans. *Pestic. Monit. J.* **11**, 61-63.
- Kutz, F. W., Strassman, S. C., Sperling, J. F., Cook, B. T., Sunshine, I., and Tessari, J. (1983). A fatal chlordane poisoning. *J. Toxicol. Clin. Toxicol.* **20**, 167-174.
- Kutz, F. W., Strassman, S. C., Stroup, C. R., Carra, J. S., Leininger, C. C., Watts, D. C., and Sparacino, C. M. (1985). The human body burden of mirex in the south eastern United States. *J. Toxicol. Environ. Health* **15**, 385-394.
- Kuwabara, N., and Takayama, S. (1974). Comparison of histogenesis of liver in mice administered respectively BHC, DDT, and 2,7-FAA. *Proc. Jpn. Cancer Assoc.* **33**, 50 (in Japanese).
- Kawahara, Y., Koga, Y., Yamaguchi, S., Matsumoto, H., Matsuo, S., Kaku, S., Tateishi, M., Shiramizu, M., Ide, I., Goto, K., Karatsu, M., and Hinagata, K. (1972). Epidemiological study of pesticide pollution. I. Organochlorine pollution. *Jpn. J. Hyg.* **27**, 103 (in Japanese).
- Kuz'minskaya, U. A., Klisenko, M. A., and Khaykina, B. I. (1972a). Peculiarities of the distribution of some pesticides in the lipid fractions of the liver. *Vopr. Pitan.* **31**, 48-52 (in Russian).
- Kuz'minskaya, U. A., Novachik, V., and Klisenko, M. A. (1972b). Distribution of polychlorocamphene in lipid fractions of tissues. *Gig. Sanit.* **37**, 96-97 (in Russian).
- Kuz'minskaya, U. A., Yakushko, V. E., Bersan, L. V., and Vercmenko, L. M. (1980). Study of the complex action of poly(chlorocamphene) using the orthogonal experimental design method. *Gig. Sanit.* **82**-83 (in Russian).
- Kveseth, N. J., Bjerk, J. E., Fimreite, N., and Stenersen, J. (1979). Residues of DDT in a Norwegian fruitgrowing district two and four years after the termination of DDT usage. *Arch. Environ. Contam. Toxicol.* **8**, 201-212.
- Kwano, M., and Tatsukawa, R. (1982). Chlordanes and related compounds in blood of pest control operators. *Nippon Noei Kagaku Kaishi* **56**, 923-929 (in Japanese).
- Kwoczek, J. (1950). Toxicity of DDT and hexachlorocyclohexane preparations. *Med. Monatsschr.* **4**, 25-28 (in German).
- Lacassagne, A. (1971). Critical review of experimental tumours of Leydig cells, more particularly in the rat. *Bull. Cancer* **58**, 235-276 (in French).
- Lackey, R. W. (1949). Observations on the acute and chronic toxicity of toxaphene in the dog. *J. Ind. Hyg. Toxicol.* **31**, 117-120.
- Lacombe, R., and Brodeur, J. (1974). The effect of pretreatment with dieldrin on certain *in vivo* parameters of enzyme induction in mice. *Toxicol. Appl. Pharmacol.* **27**, 70-85.
- Lakkad, B. C., Nigam, S. K., Karnik, A. B., Thakora, K. N., Aravindra Babu, K., Blatt, D. K., and Kashyap, S. K. (1982). Dominant-lethal study of technical-grade hexachlorocyclohexane in Swiss mice. *Mutat. Res.* **101**, 315-320.
- Lamartiniere, C. A., Luther, M. A., Lucier, G. W., and Illsley, N. P. (1982). Altered imprinting of rat liver monoamine oxidase by  $o,p'$ -DDT and methoxychlor. *Biochem. Pharmacol.* **31**, 647-651.
- Lamoureux, C. H., and Feil, V. J. (1980). Gas chromatographic and mass spectrometric characterization of impurities in technical methoxychlor. *J. Assoc. Off. Anal. Chem.* **63**, 1007-1037.
- Landoui, J. H., and Astolfi, E. A. (1982). Organochlorinated pesticides residues in human milk—Rep. Argentina—10 years monitoring. *Pap. Int. Symp., Chem. Environ., Copenhagen*, 1982.
- Lang, B., and Maier, P. (1986). Lipid peroxidation dependent aldrin epoxidation in liver microsomes, hepatocytes and granulosa tissue cells. *Biochem. Biophys. Res. Commun.* **138**, 24-32.
- Lang, B., Frei, K., and Maier, P. (1986). Prostaglandin synthase dependent aldrin epoxidation in hepatic and extrahepatic tissue of rats. *Biochem. Pharmacol.* **35**, 3643-3645.
- Lange, M., Nitzsche, K., and Zesch, A. (1981). Percutaneous absorption of lindane in healthy volunteers and scabies patients. *Arch. Dermatol. Res.* **271**, 387-399.
- Larsen, A. A., Robinson, J. M., Schmitt, N., and Hole, L. (1971). Pesticide residues in mother's milk and human fat from intensive use of soil insecticides. *HSMHA Health Rep.* **86**, 477-481.
- Larson, P. S., Hennigar, G. R., Finnegan, J. K., Smith, R. B., Jr., and Haag, H. B. (1955). Observations on the relation of chemical structure to the production of adrenal cortical atrophy or hypertrophy in the dog by derivatives of 2,2-bis(p-chlorophenyl)-1,1-dichloroethane (DDD, TDE). *J. Pharmacol. Exp. Ther.* **115**, 408-412.
- Larson, P. S., Egle, J. L., Jr., Hennigar, G. R., Lane, R. W., and Borzelleca, J. F. (1979a). Acute, subchronic, and chronic toxicity of chlordecone. *Toxicol. Appl. Pharmacol.* **48**, 29-41.
- Larson, P. S., Egle, J. L., Jr., Hennigar, G. R., and Borzelleca, J. F. (1979b). Acute and subchronic toxicity of mirex in the rat, dog, and rabbit. *Toxicol. Appl. Pharmacol.* **49**, 271-277.
- Laug, E. P., Nelson, A. A., Fitzhugh, O. G., and Kunze, F. M. (1950). Liver-cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1 to 50 ppm of DDT. *J. Pharmacol. Exp. Ther.* **98**, 268-273.
- Laug, E. P., Kunze, F. M., and Prickett, C. S. (1951). Occurrence of DDT in human fat and milk. *Arch. Ind. Hyg. Occup. Med.* **3**, 245-246.
- Laüger, P., Martin, H., and Müller, P. (1944). Constitution and toxic effects of natural and synthetic insecticides. *Helv. Chim. Acta* **27**, 892-928 (in German).
- Laüger, P., Pulver, R., and Montigel, C. (1945a). Mode of action of 4,4'-dichlorodiphenyl-trichloromethyl-methane (DDT-Geigy) in warm-blooded organisms. *Experientia* **1**, 120-121 (in German).
- Laüger, P., Pulver, R., and Montigel, C. (1945b). Mode of action of 4,4'-dichlorodiphenyl-trichloromethyl-methane (DDT-Geigy) in warm-blooded animals. *Helv. Physiol. Pharmacol. Acta* **3**, 405-415 (in German).
- Lawrence, L. J., and Casida, J. E. (1984). Interactions of lindane, toxaphene and cyclodienes with brain specific *t*-butylcyclophosphorothionate receptor. *Life Sci.* **35**, 171-178.
- Laws, E. R., Jr. (1971). Evidence of antitumorigenic effects of DDT. *Arch. Environ. Health* **23**, 181-183.
- Laws, E. R., Jr., Curley, A., and Biros, F. J. (1967). Men with intensive occupational exposure to DDT. A clinical and chemical study. *Arch. Environ. Health* **15**, 766-775.
- Laws, E. R., Maddrey, W. D., Curley, A., and Burse, V. W. (1973). Long-term occupational exposure to DDT. *Arch. Environ. Health* **27**, 318-321.
- Lay, J. P., Weisgerber, I., and Klein, W. (1975). Conversion of the aldrin/dieldrin metabolite dihydrochlordene dicarboxylic acid-<sup>14</sup>C in rats. *Pestic. Biochem. Physiol.* **5**, 226-232.
- Lay, J. P., Klein, W., Korte, F., and Richter, E. (1981). Metabolism of  $\beta$ -hexachlorocyclohexane-<sup>14</sup>C in rats following low dosing in the diet. *J. Environ. Sci. Health, Part B* **16**, 227-238.
- Leach, J. F., and Charles, A. K. (1987). Regional mirex distribution and its effects on  $\gamma$ -aminobutyric acid and flunitrazepam binding in mouse strains. *J. Toxicol. Environ. Health* **21**, 423-433.
- Lee, B., and Groth, P. (1977). Scabies: Transcutaneous poisoning during treatment. *Pediatrics* **59**, 643.
- Lee, B., Groth, P., and Turner, W. (1976). Suspected reactions to benzene hexachloride. *JAMA, J. Am. Med. Assoc.* **236**, 2846.
- Lee, M., Harris, K., and Trowbridge, H. (1964). Effect of the level of dietary protein on the toxicity of dieldrin for the laboratory rat. *J. Nutr.* **84**, 136-144.
- Lehman, A. J. (1948). The toxicology of the new agricultural chemicals. *Q. Bull.—Assoc. Food Drug Off.* **12**, 82.
- Lehman, A. J. (1950). Some toxicological reasons why certain chemicals may or may not be permitted as food additives. *Q. Bull.—Assoc. Food Drug Off.* **14**, 82-98.
- Lehman, A. J. (1951). Chemicals in foods: A report to the Association of Food and Drug Officials on current developments. Part II. Pesticides. Section I: Introduction. *Q. Bull.—Assoc. Food Drug Off.* **15** (I), 122-125. Lehman, A. J. (1952). Chemicals in foods: A report to the Association of Food and Drug officials on current developments. Part II. Pesticides. Section II. Dermal toxicity. Section III. Subacute and chronic toxicity. Section IV. Biochemistry. Section V. Pathology. *Q. Bull.—Assoc. Food Drug Off.* **16** (II), 3-9; (III), 47-53; (IV), 85-91; (V), 126-132.
- Lehman, A. J. (1965). "Summaries of Pesticide Toxicity." Assoc. Food Drug Off. U.S., Topeka, Kansas.
- Leighty, E. G. (1981). Decreased retention of fatty acid conjugated DDT metabolites in rats given injections of heparin, bile salts or leirithin. *Res. Commun. Chem. Pathol. Pharmacol.* **31**, 69-76.
- Leighty, E. G., Fentiman, A. F., and Thompson, R. M. (1980). Conjugation of fatty acids to DDT in the rat: Possible mechanism for retention. *Toxicology* **15**, 77-82.
- LeMarchand, L., Kolonel, L. N., Siegel, B., and Dendle, W. H. (1986). Trends in birth defects for a Hawaiian population exposed to heptachlor and for the United States. *Arch. Environ. Health* **41**, 145-148.
- Lemmon, G. B., and Pierce, W. F. (1952). Intoxication due to chlordane. Report of a case. *JAMA, J. Am. Med. Assoc.* **149**, 1314-1316.
- Lensky, G. B., and Pierce, W. F. (1952). Human poisoning by chlordane. Report of a case. *JAMA, J. Am. Med. Assoc.* **149**, 1394-1395.
- Leshchenko, P. D., and Polonskaia, M. N. (1969). New products in the



- prophylactic nutrition of workers in the organochlorine industry. *Vrach. Delo* **8**, 106-110 (in French).
- Levy, J. M., Lutz, P., Wagner, C., Sauer, P., Seiller, F., Fischbach, M., Segura, N., and Sauvage, P. (1985). Favorable outcome of a recurring malignant adrenocortical tumor under *o,p'*-DDD therapy. *Ann. Pediatr.* **32**, 541-544 (in French).
- Levy, K. A., Brady, S. E., and Pfaffenberger, C. D. (1981). Chlorobenzilate residues in citrus-workers. *Bull. Environ. Contam. Toxicol.* **27**, 235-238.
- Lewis, W. H., and Richards, A. G., Jr. (1945). Non-toxicity of DDT on cells in cultures. *Science* **102**, 330-331.
- Lidov, R. E., Bluestone, H., and Soloway, S. B. (1950). Alkali-stable polychloro-organic insect toxicants, aldrin and dieldrin. *Adv. Chem.* **1**, 175-183.
- Lièvreumont, M., and Potus, J. (1981). Intracerebral distribution of lindane in the rat; observations a short time after single dose administration. *C.R. Seances Acad. Sci., Ser. 3* **292**, 1163-1168 (in French).
- Lièvreumont, M., Barnier, J. V., and Potus, J. (1984).  $\gamma$ -Hexachlorocyclohexane inhibition of the calcium fluxes at the desensitized mouse neuromuscular junction. *Toxicol. Appl. Pharmacol.* **76**, 280-287.
- Lillie, R. D., and Smith, M. I. (1944). Pathology of experimental poisoning in cats, rabbits, and rats with 2,2-bis-(para-chlorophenyl)-1,1,1-trichloroethane. *Public Health Rep.* **59**, 979-984.
- Lillie, R. D., Smith, M. I., and Stohlman, E. F. (1947). Pathologic action of DDT and certain of its analogs and derivatives. *Arch. Pathol.* **43**, 127-142.
- Lillie, R. J., Cecil, H. C., and Bitman, J. (1973). Methoxychlor in chicken breeder diets. *Poult. Sci.* **52**, 1134-1138.
- Linder, R. E., Scotti, T. M., McElroy, W. K., Laskey, J. W., Straceler, L. F., and Powell, K. (1983). Spermatotoxicity and tissue accumulation of chlordane (Kepone) in male rats. *J. Toxicol. Environ. Health* **12**, 183-192.
- Linder, R. L., Dahlgren, R. B., and Greichus, Y. A. (1970). Residues in the brain of adult pheasants given dieldrin. *J. Wildl. Manage.* **34**, 954-956.
- Litterst, C. L., Miller, E., Michel, T., Olivito, V., and Van Loon, E. J. (1973). Distribution and penetration of lindane into brains of normal and phenobarbital pretreated dogs. *Toxicol. Appl. Pharmacol.* **25**, 484-485.
- Litvinov, N. N., and Nikonova, A. G. (1971). The action of alkyl sulfate on the resorption of pesticides and on their content in animal organs. *Gig. Sanit.* **36**, 21-25 (in Russian).
- Liu, P. T., and Morgan, D. P. (1986). Comparative toxicity and biotransformation of lindane in C57BL/6 and DBA/2 mice. *Life Sci.* **39**, 1237-1244.
- Llinares, V. M., and Wasserman, M. (1968). Storage of DDT in the body fat of the people of Spain. Unpublished data (cited by Wassermann *et al.*, 1968b).
- Lockard, V. G., Mehendale, H. M., and O'Neal, R. M. (1983a). Chlordane-induced potentiation of carbon tetrachloride hepatotoxicity: A light and electron microscopic study. *Exp. Mol. Pathol.* **39**, 230-245.
- Lockard, V. G., Mehendale, H. M., and O'Neal, R. M. (1983b). Chlordane-induced potentiation of carbon tetrachloride hepatotoxicity: A morphometric and biochemical study. *Exp. Mol. Pathol.* **39**, 246-255.
- Loeber, J. G., and Van Velsen, F. L. (1984). Uterotropic effect of beta-HCH, a food chain contaminant. *Food Addit. Contam.* **1**, 63-66.
- Loevinsohn, M. E. (1987). Insecticide use and increased mortality in rural central Luzon, Philippines. *Lancet* **1**, 1359-1362.
- Lofroth, G. (1968). Pesticides and catastrophe. *New Sci.* **40**, 567-568.
- Loganovskii, N. G. (1971). The effect of hexachlorane on the functional state of the kidneys. *Gig. Tr. Prof. Zabol.* **15**, 46-48.
- Loge, J. P. (1965). Aplastic anemia following exposure to benzene hexachloride (lindane). *JAMA, J. Am. Med. Assoc.* **193**, 110-114.
- Loose, L. D. (1982). Macrophage induction of T-suppressor cells in pesticide-exposed and protozoan-infected mice. *Environ. Health Perspect.* **43**, 89-97.
- Lopez-Aparicio, P., Del Hoyo, N., and Perez-Albarsanz, M. A. (1988). Lindane distribution and phospholipid alterations in rat tissues after administration of lindane-containing diet. *Pestic. Biochem. Physiol.* **31**, 109-119.
- Lu, F. C., Jessup, D. C., and Lavalley, A. (1965). Toxicity of pesticides in young versus adult rats. *Food Cosmet. Toxicol.* **3**, 591-596.
- Lubberink, A. A. M. E., Rijnberk, A., Der Kinderen, P. J., and Thijssen, J. H. H. (1971). Hyperfunction of the adrenal cortex: A review. *Aust. Vet. J.* **47**, 504-509.
- Lubitz, J. A., Feeman, L., and Okum, R. (1973). Mitotane use in inoperable adrenal cortical carcinoma. *JAMA, J. Am. Med. Assoc.* **233**, 1109-1112.
- Ludke, J. L. (1974). Interaction of dieldrin and DDE residues in Japanese quail (*Coturnix coturnix japonica*). *Bull. Environ. Contam. Toxicol.* **11**, 297-302.
- Luis, P. (1952). A case of detection of DDT in viscera. *Rev. Asoc. Bloquim. Argent.* **17**, 334-338 (in Spanish).
- Lund, B., Klasson-Wehler, F., and Brandt, I. (1986). *o,p'*-DDD in the mouse lung: Selective uptake, covalent binding and effect on drug metabolism. *Chem.-Biol. Interact.* **60**, 129-141.
- Lund, B., Bergman, A., and Brandt, I. (1988). Metabolic activation of a DDT-metabolite, 3-methylsulfonyl-DDE, in the adrenal *zona fasciculata* in mice. *Chem.-Biol. Interact.* **65**, 24-40.
- Lund, B. O., Ghanous, H., Bergman, A., and Brandt, I. (1989). Covalent binding of four DDD isomers in the mouse lung: Lack of structure specificity. *Pharmacol. Toxicity.* **65**, 282-286.
- Luquet, F. M., Goursaud, J., and Gaudier, B. (1972). Study of the pollution of human milk by residual pesticides. *Pathol. Biol.* **20**, 137-143 (in French).
- Luquet, F. M., Goursaud, J. G., and Casalis, J. (1974a). Residues of organochlorine pesticides in the milk of animals and humans. *Ann. Falsif. Expert. Chim.* **67**, 217-239 (in French).
- Luquet, F. M., Goursaud, J. G., and Casalis, J. (1974b). Residues of organochlorine pesticides in the milk of animals and humans. *Lait* **54**, 269-301 (in French).
- Luton, J. P., Valcke, J. C., Remy, J. M., Mathieu de Fossey, B., and Bricaire, H. (1972). Gynecomastia after long-term treatment of Cushing's disease with *o,p'*-DDT. *Ann. Endocrinol.* **33**, 290-293 (in French).
- Luton, J. P., Remy, J. M., Valcke, J. C., Laudat, P., and Bricaire, H. (1973). Cure or remission of Cushing's disease by prolonged therapeutic use of *o,p'*-DDD (with reference to 17 observations). *Ann. Endocrinol.* **34**, 351-376 (in French).
- Lyubchenko, P. N., Chemnyy, A. B., Boyarchuk, Z. I., Ginzburg, D. A., and Sukova, V. M. (1973). Effects of a BHC-thiram combination in humans. *Gig. Tr. Prof. Zabol.* **17**, 50-52 (in Russian).
- Lyubchenko, P. K., Stefanskiy, K. S., and Rosenfel'd, A. A. (1973a). Procedure in using polychlorocamphene in agriculture and its content in soil and plants. *Khim. Sel'sk. Khoz.* **11**, 28-29 (in Russian).
- Lyubchenko, P. K., Stefanskiy, K. S., and Rozenfel'd, A. A. (1973b). Regulations for polychlorocamphene use in agriculture and content of it in soil and plants. *Khim. Sel'sk. Khoz.* **11**, 908-909 (in Russian).
- MacCormack, J. D. (1945). Infestation and DDT. *Ir. J. Med. Sci.* **6**, 627-634.
- Macek, K. J., Rodgers, C. R., Stalling, D. L., and Korn, S. (1970). The uptake, distribution, and elimination of dietary 14-C-DDT and 14-C-dieldrin in rainbow trout. *Trans. Am. Fish. Soc.* **99**, 689-695.
- Macholz, R. M., and Kujawa, M. (1985). Recent state of lindane metabolism. Part III. *Residue Rev.* **94**, 119-149.
- Macholz, R. M., Knoll, R., Lewerenz, H. J., Petrzika, M., and Engst, R. (1982a). Metabolism of  $\alpha$ -hexachlorocyclohexane. Free metabolites in urine and organs of rats. *Xenobiotica* **12**, 227-231.
- Macholz, R. M., Knoll, R., Lewerenz, H. J., and Plass, R. (1982b). Biodegradation of beta-hexachlorocyclohexane. Free metabolites in rat urine and organs. *Arch. Toxicol.* **50**, 85-88.
- Macholz, R. M., Seidler, H., Petrzika, M., and Kujawa, J. (1985). Identification of an amino acid conjugate in the urine following administration of lindane to rats. *Z. Gesamte Hyg. Ihre Grenzgeb.* **31**, 177-178 (in German).
- Macholz, R. M., Bleyl, D. W. R., Klepel, H., Knoll, R., Kujawa, M., Lewerenz, H. J., Mueller, D., and Plass, R. (1986). Comparison of distribution and toxicity of  $\alpha$ -,  $\beta$ - and  $\gamma$ -hexachlorocyclohexane (HCH) after application to rats for 30 days. *Nahrung* **30**, 701-708 (in German).
- Mackerras, I. M., and West, R. F. K. (1946). "DDT" poisoning in man. *Med. J. Aust.* **1**, 400-401.
- Macklin, A. W., and Ribelin, W. E. (1971). The relation of pesticides to abortion in dairy cattle. *J. Am. Vet. Med. Assoc.* **159**, 1743-1748.
- MacMahon, B. (1985). Phenobarbital: Epidemiological evidence. *IARC Sci. Publ.* **65**, 101-105.
- MacNamara, B. G. P. (1970). Benzene hexachloride poisoning. *Br. Med. J.* **3**, 585.
- Mactutus, C. F., and Tilson, H. A. (1984a). Evaluation of neonatal chlordane neurotoxicity during early development. *Neurobehav. Toxicol. Teratol.* **6**, 67-73.
- Mactutus, C. F., and Tilson, H. A. (1984b). Neonatal chlordane exposure impairs early learning and retention of active avoidance in the rat. *Neurobehav. Toxicol. Teratol.* **6**, 75-83.
- Maes, R., and Heyndrickx, A. (1966). Distribution of organic chlorinated insecticides in human tissues. *Meded. Rijksfac. Landbouw wet. Gent* **31**, 1021-1025.
- Magour, S., Mäser, H., and Steffen, I. (1984). Effect of lindane on synaptosomal  $\text{Na}^+/\text{K}^+$ -ATPase in relation to its subcellular distribution in the brain. *Acta Pharmacol. Toxicol.* **54**, 299-303.
- Mahmood, A., Agarwal, N., Sanyal, S., Dudeja, P. K., and Subrahmanyam, D. (1981). Acute dieldrin toxicity effect on the uptake of glucose and leucine on brush border enzymes in monkey intestine. *Chem.-Biol. Interact.* **37**, 165-170.
- Maier-Bode, H. (1960). DDT in body fat of people. *Med. Exp.* **1**, 146-152 (in German).
- Maier-Bode, H. (1968). Properties, effect, residues and analytics of the insecticide endosulfan. *Residue Rev.* **22**, 1-44.
- Majumdar, S. K., Kopleman, H. A., and Schnitman, M. J. (1976). Dieldrin-induced chromosome damage in mouse bone-marrow and WI-38 human lung cells. *J. Hered.* **67**, 303-307.
- Makara, G. (1973). Chlorphenamide as an ovicide and the efficiency of heat in killing lice and nits. *Sci. Publ.—Pan. Am. Health Organ.* **263**, 198-200.
- Makovskaya, Y. I., Shamray, P. F., and Grigor'yeva, N. N. (1972). Structural and histochemical changes in internal secretion glands during polychloropine poisoning. *Vrach. Delo* **2**, 128-131 (in Russian).
- Mal'tseva, Z. I., and Savchuk, T. F. (1953). The possibility of chronic poisoning with the use of BHC for disinfection of habitable dwellings. *Gig. Sanit.* **12**, 43-45 (in Russian).
- Mandroui, V., and Iordachescu, M. (1971). Determination of the BHC content in the human organism. *Igiene* **20**, 363-364 (in Romanian).
- Marchand, M., Dubrulle, P., and Goudemand, M. (1956). Agranulocytosis in a subject exposed to vapor of hexachlorocyclohexane. *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **17**, 256-258 (in French).
- Maresch, W., Lembeck, F., and Lipp, W. (1960). Poisonings in infancy. *Wien Klin. Wochenschr.* **72**, 411-416 (in German).
- Markarian, D. S. (1966). Cytogenetic effect of some chlorine-containing organic insecticides on mouse bone-marrow cell nuclei. *Genetika* **1**, 132-137.
- Marquardt, E. D. (1982). Suicide attempt with rectally administered chlordane. *Drug Intell. Clin. Pharm.* **16**.
- Martinez, A. J., Taylor, J. R., Dyck, P. J., Jouff, S. A., and Isaacs, E. (1978). Chlordane intoxication in man. II. Ultrastructure of peripheral nerves and skeletal muscle. *Neurology* **28**, 631-635.
- Martson, L. V., and Shepel'skaya, N. R. (1980). Study of the reproductive function in animals exposed to polychlorocamphene. *Gig. Sanit.*, pp. 14-16 (in Russian).
- Martz, F., and Straw, J. A. (1972). Effects of mitotane (*o,p'*-DDD) on hepatic drug metabolism in dogs. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **31**, 581.
- Martz, F., and Straw, J. A. (1973). Mitotane decreases adrenal cortical heme and P450. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **32**, 734.
- Martz, F., and Straw, J. A. (1977). The *in vitro* metabolism of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane (*o,p*-DDD) by dog adrenal mitochondria and metabolite covalent binding to mitochondrial macromolecules. A possible mechanism for the adrenocorticolytic effect. *Drug. Metab. Dispos.* **5**, 482-486.
- Martz, F., and Straw, J. A. (1980). Metabolism and covalent binding of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane (*o,p*-DDD). Correlation between adrenocorticolytic activity and metabolic activation by adrenocortical mitochondria. *Drug Metab. Dispos.* **8**, 127-130.
- Maslansky, C. J., and Williams, G. M. (1981). Evidence for an epigenetic mode of action in organochlorine pesticide hepatocarcinogenicity: A lack of genotoxicity in rat, mouse, and hamster hepatocytes. *J. Toxicol. Environ. Health* **8**, 121-130.
- Mason, T. J., McKay, F. W., Hoover, F., Blot, W. J., and Fraumeni, J. F., Jr. (1975). "Atlas of Cancer Mortality for U. S. Counties: 1950-1969." Publ. No. (NIH) 75-780. U.S. Department of Health, Education and Welfare, Public Health Service, Washington, D. C.
- Matsuda, H., Shimamoto, T., Ito, T., and Ogida, K. (1971). On the analytical results of organochlorine pesticide residues in mothers' milk. *Annu. Rep. Ehime Prefect. Hyg. Lab.* **33**, 43-48 (in Japanese).
- Matsumura, F., and Ghiasuddin, S. M. (1983). Evidence for similarities between cyclodiene type insecticides and picrotoxin in their action mechanisms. *J. Environ. Sci. Health, Part B*, **B18**, 1-14.
- Matsumura, F., and Patil, K. C. (1969). Adenosine triphosphatase sensitive to DDT in synapses of rat brain. *Science* **166**, 121-122.
- Matsumura, F., and Nelson, J. O. (1970). Identification of the major metabolic product of heptachlor epoxide in rat feces. *Bull. Environ. Contam. Toxicol.* **5**, 489-492.
- Matsumura, F., Patil, K. C., and Bousch, G. M. (1970). Formation of "photodieldrin" by microorganisms. *Science* **170**, 1206-1207.
- Matsumura, F., Howard, R. W., and Nelson, J. O. (1975). Structure of the toxic fraction A of toxaphene. *Chemosphere* **5**, 271-276.
- Matsunaga, K., Ogino, Y., Morita, K., Sueishi, T., Imanaka, M., Mukada, K., Namba, S., Tada, Y., and Takata, M. (1975). Hygienic studies on pesticide residues. Part 3. Organochlorine pesticide residues in human milk. *Annu. Rep. Hyg. Lab. Okayama Prefect.* **22**, 35-38 (in Japanese).
- Matsuoka, L. Y. (1981). Convulsions following application of gamma benzene hexachloride. *J. Am. Acad. Dermatol.* **5**, 98-99.
- Matthews, H. B., and Matsumura, F. (1969). Metabolic fate of dieldrin in the rat. *J. Agric. Food Chem.* **17**, 845-852.
- Matthews, H. B., and McKinney, J. D. (1974). Dieldrin metabolism to *cis*-dihydroaldrindiol and epimerization of *cis*- to *trans*-dihydroaldrindiol by rat liver microsomes. *Drug Metab. Dispos.* **2**, 333-340.
- Matthews, H. B., McKinney, J. D., and Lucier, G. W. (1971). Dieldrin metabolism, excretion, and storage in male and female rats. *J. Agric. Food Chem.* **19**, 1244-1248.
- Matthews, H. B., Domanski, J. J., and Guthrie, F. E. (1976). Hair and its associated lipids as an excretory pathway for chlorinated hydrocarbons. *Xenobiotica* **6**, 425-429.
- Mattson, A. M., Spillane, J. T., Baker, C., and Pearce, G. W. (1953). Determination of DDT and related substances in human fat. *Anal. Chem.* **25**, 1065-1070.
- Matuo, Y. K., Lopes, J. N., and Lopes, J. L. (1980). DDT levels in human milk from Ribeirao Preto (Brazil). *Rev. Bras. Biol.* **40**, 293-296 (in Portuguese).
- Mayer, F. L., Street, J. C., and Neubold, J. M. (1970). Organochlorine insecticide interactions affecting residue storage in rainbow trout. *Bull. Environ. Contam. Toxicol.* **5**, 300-310.
- Mayer, R. T., and Himel, C. M. (1972). Dynamics of fluorescent probe-cholinesterase reactions. *Biochemistry* **11**, 2082-2090.
- Mayersdorf, A., and Israeli, R. (1974). Toxic effects of chlorinated hydrocarbon insecticides on the human electroencephalogram. *Arch. Environ. Health* **28**, 159-163.
- McBlain, W. A. (1987). The levo enantiomer of *o,p'*-DDT inhibits the binding of  $^{125}\text{I}$ -estradiol to the estrogen receptor. *Life Sci.* **40**, 215-221.
- McCann, J., and Ames, B. N. (1976). Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals: Discussion. *Proc. Natl. Acad. Sci. U.S.A.* **73**, 950-954.
- McCann, J., Chol, E., Yamasaki, E., and Ames, B. N. (1975). Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc. Natl. Acad. Sci. U.S.A.* **72**, 5135-5139.
- McGee, L. C., Reed, H. L., and Fleming, J. P. (1952). Accidental poisoning by toxaphene. Review of toxicology and case reports. *JAMA, J. Am. Med. Assoc.* **149**, 1124-1126.
- McKiernan, P., Doyle, D. A., Duffy, G. J., Towers, R. P., Duff, F. A., and O'Donovan, D. K. (1978). Brief report. *o,p'*-DDD and adrenal carcinoma. *Ir. J. Med. Sci.* **147**, 437-440.



- McKinney, J. D., Boozier, E. L., Hopkins, H. P., and Suggs, J. E. (1969). Synthesis and reactions of a proposed DDT metabolite, 2,2'-bis-(p-chlorophenyl)-acetaldehyde. *Experientia* **25**, 897-898.
- McKinney, J. D., Matthews, H. B., and Fishbein, L. (1972). Major fecal metabolite of dieldrin in rat. Structure and chemistry. *J. Agric. Food Chem.* **20**, 597-602.
- McLachlan, J. A., and Dixon, R. L. (1972). Gonadal function in mice exposed prenatally to p,p'-DDT. *Toxicol. Appl. Pharmacol.* **22**, 327.
- McLean, J. A. (1966). Aplastic anaemia associated with insecticides. *Med. J. Aust.* **1**, 996.
- McManus, M. E., Boobis, A. R., Minchin, R. F., Schwartz, D. M., Murray, S., Davies, D. S., and Thorgeirsson, S. S. (1984). Relationship between oxidative metabolism of 2-acetylaminofluorene, debrisoquine, bifuralol, and aldrin in human liver microsomes. *Cancer Res.* **44**, 5692-5697.
- McNamara, B. P., and Krop, S. (1948a). Observations on the pharmacology of the isomers of hexachlorocyclohexane. *J. Pharmacol. Exp. Ther.* **92**, 140-146.
- McNamara, B. P., and Krop, S. (1948b). The treatment of acute poisoning produced by gamma hexachlorocyclohexane. *J. Pharmacol. Exp. Ther.* **92**, 147-152.
- McQueen, E. G., Brosnan, C., and Ferry, D. G. (1968). Poisoning from a rose spray containing lindane and malathion. *N. Z. Med. J.* **67**, 533-537.
- McQueen, E. G., Owen, D., and Ferry, D. G. (1972). Effect of phenytoin and other drugs in reducing serum DDT levels. *N. Z. Med. J.* **75**, 208-211.
- Mead, R. J. (1982). Lindane, Kwell and aplastic anemia. *Postgrad. Med.* **72**, 28.
- Medley, J. G., Bond, C. A., and Woodham, D. W. (1974). The cumulation and disappearance of mirex residues. I. In tissues of roosters fed four concentrations of mirex in their feed. *Bull. Environ. Contam. Toxicol.* **11**, 217-223.
- Mehendale, H. M. (1977a). Chemical reactivity-absorption, retention, metabolism, and elimination of hexachlorocyclopentadiene. *Environ. Health Perspect.* **21**, 275-278.
- Mehendale, H. M. (1977b). Effect of preexposure to Kepone on the biliary excretion of imipramine and sulfbromophthalein. *Toxicol. Appl. Pharmacol.* **40**, 247-259.
- Mehendale, H. M. (1977c). Mirex-induced impairment of hepatobiliary function. Suppressed biliary excretion of imipramine and sulfbromophthalein. *Drug Metab. Dispos.* **5**, 56-62.
- Mehendale, H. M. (1978). Pesticide-induced modification of hepatobiliary function: Hexachlorobenzene, DDT and toxaphene. *Food Cosmet. Toxicol.* **16**, 19-25.
- Mehendale, H. M. (1981b). Chlordane-induced hepatic dysfunction. *J. Toxicol. Environ. Health* **8**, 743-755.
- Mehendale, H. M. (1989). Mechanism of the lethal interaction of chlordane and CCl<sub>4</sub> at non-toxic doses. *Toxicol. Lett.* **49**, 215-241.
- Mehendale, H. M., and El-Bassiouni, E. A. (1975). Uptake and disposition of aldrin and dieldrin by isolated perfused rabbit lung. *Drug. Metab. Dispos.* **3**, 543-556.
- Mehendale, H. M., and Klingensmith, J. C. (1988). *In vivo* metabolism of CCl<sub>4</sub> by rats pretreated with chlordane, mirex, or phenobarbital. *Toxicol. Appl. Pharmacol.* **93**, 247-256.
- Mehendale, H. M., Fishbein, L., Fields, M., and Matthews, H. B. (1972). Fate of mirex-<sup>14</sup>C in the rat and plants. *Bull. Environ. Contam. Toxicol.* **8**, 200-207.
- Mehendale, H. M., Chen, P. F., Fishbein, L., and Matthews, H. B. (1973). Effect of mirex on the activities of various rat hepatic mixed-function oxidases. *Arch. Environ. Contam. Toxicol.* **1**, 245-254.
- Mehendale, H. M., El-Bassiouni, E. A., and McKinney, J. D. (1974). Disposition of aldrin by isolated perfused rabbit lung preparations. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **33**, 534.
- Mehendale, H. M., Takanaka, A., Desai, D., and Ho, I. K. (1977). Kepone induction of hepatic mixed function oxidases. *Life Sci.* **20**, 991-998.
- Mehendale, H. M., Takanaka, A., Desai, D., and Ho, I. K. (1978). Effect of preexposure to kepone on hepatic mixed function oxidases in the female rat. *Toxicol. Appl. Pharmacol.* **44**, 171-180.
- Mehendale, H. M., Ho, I. K., and Desai, D. (1979). Possible molecular mechanism of mirex-induced hepatobiliary dysfunction. *Drug Metab. Dispos.* **7**, 28-33.
- Mehendale, H. M., Purushotham, K. R., and Lockard, V. G. (1989). The time course of liver injury and [<sup>3</sup>H]thymidine incorporation in chlordane-potentiated CHCl<sub>3</sub> hepatotoxicity. *Exp. Mol. Pathol.* **51**, 31-47.
- Mehrota, B. D., Bansal, S. K., and Desai, D. (1982). Comparative effects of structurally related cyclodiene pesticides on ATPases. *J. Appl. Toxicol.* **2**, 278-283.
- Meierhenry, E. F., Reubner, B. H., Gershwin, M. E., Hsieh, L. S., and French, S. W. (1983). Dieldrin-induced Mallory bodies in hepatic tumors of mice of different strains. *Hepatology* **3**, 90-95.
- Mellis, R. (1955). Tolerability of small doses of lindane by warm-blooded animals. *Nuovi Ann. Ig. Microbiol.* **6**, 90.
- Menconi, S., Clark, J. M., Langenberg, P., and Hryhorczyk, D. (1988). A preliminary study of potential human health effects in private residences following chlordane applications for termite control. *Arch. Environ. Health* **43**, 349-352.
- Menczel, E., Bucks, D., Maibach, H., and Wester, R. (1984). Lindane binding to sections of human skin: Skin capacity and isotherm determinations. *Arch. Dermatol. Res.* **276**, 326-329.
- Mendeloff, A. I., and Smith, D. E. (1955). Exposure to insecticides, bone marrow failure, gastrointestinal bleeding, and uncontrollable infections. *Am. J. Med.* **19**, 274-284.
- Menna, J. H., Barnett, J. B., and Soderberg, L. S. (1985). Influenza type A infection of mice exposed in utero to chlordane; survival and antibody studies. *Toxicol. Lett.* **24**, 45-52.
- Menner, K. (1965). Experiences of poisonings of infants. *Med. Welt* **13**, 634-638 (in German).
- Menzie, C. M. (1969). "Metabolism of Pesticides," Spec. Sci. Rep., Wildl. No. 127. U. S. Govt. Printing Office, Washington, D.C.
- Mes, J., and Davies, D. J. (1979). Presence of polychlorinated biphenyl and organochlorine pesticide residues and the absence of polychlorinated terphenyls in Canadian human milk samples. *Bull. Environ. Contam. Toxicol.* **21**, 381-387.
- Mes, J., Campbell, D., Robinson, R., and Davis, D. (1977). Polychlorinated biphenyls and organochlorine residues in adipose tissue of Canadians. *Bull. Environ. Contam. Toxicol.* **17**, 196-203.
- Mes, J., Davies, D. J., and Miles, W. (1978). Traces of mirex in some Canadian human milk samples. *Bull. Environ. Contam. Toxicol.* **19**, 564-570.
- Mes, J., Davis, D. J., and Turton, D. (1982). Polychlorinated biphenyl and other chlorinated hydrocarbon residues in adipose tissue of Canadians. *Bull. Environ. Contam. Toxicol.* **28**, 97-104.
- Mes, J., Davies, D. J., Turton, D., and Sun, W. (1986). Levels and trends of chlorinated hydrocarbon contaminants in the breast milk of Canadian women. *Food Addit. Contam.* **3**, 313-322.
- Mestitzová, M. (1967). On reproduction studies and the occurrence of cataracts in rats after long-term feeding of the insecticide heptachlor. *Experientia* **23**, 42-43.
- Mestitzová, M., and Beňo, M. (1966). Toxicologic characteristics of small repeated doses of heptachlor. *Prac. Lek.* **18**, 153-157 (in Slovakian).
- Mestitzová, M., Kovac, J., and Durcek, K. (1970a). Heptachlor induced changes in fenitrothion metabolism. *Bull. Environ. Contam. Toxicol.* **5**, 195-201.
- Mestitzová, M., Kovac, J., Durcek, K., and Hladka, A. (1970b). Toxicity of an organophosphate (fenitrothion) in rats chronically poisoned with an organochlorine (heptachlor). *Prac. Lek.* **22**, 361-365.
- Mestitzová, M., Kovac, J., and Durcek, K. (1971). Metabolic studies of combinations of pesticides. *Int. Arch. Arbeitsmed.* **22**, 223-238 (in German).
- Metcalfe, R. L. (1973). A century of DDT. *J. Agric. Chem.* **21**, 511-519.
- Michail, G. (1974a). Experimental studies on toxic effects of BHC and parathion administered jointly. *J. Jpn. Assoc. Rural Med.* **22**, 772-773 (in Japanese).
- Michail, G. (1974b). On the preliminary study of occupational chronic exposure in plant protection. *J. Jpn. Assoc. Rural Med.* **22**, 773 (in Japanese).

- Michail, G., Zlavog, A., Anghelache, V., and Bodnar, J. (1972). Serum ornithine carbamoyltransferase, test for evaluating hepatic alterations caused by some industrial toxic substances. *Igiene* **21**, 267-276 (in Romanian).
- Mick, D. L., Long, K. R., Dretchen, J. S., and Bonderman, D. P. (1971). Aldrin and dieldrin in human blood components. *Arch. Environ. Health* **23**, 177-180.
- Mick, D. L., Long, K. R., and Bonderman, D. P. (1972). Aldrin and dieldrin in the blood of pesticide formulators. *Am. Ind. Hyg. Assoc. J.* **33**, 94-99.
- Micks, D. W. (1954). Potential health hazards of organic insecticides. *Tex. State J. Med.* **50**, 148-153.
- Mikosha, A. S. (1985). Effect of chlordane on activity of malate enzymes in adrenal gland. *Vopr. Med. Khim.* **31**, 61-64.
- Milby, T. H., and Samuels, A. J. (1971). Human exposure to lindane: Comparison of an exposed and unexposed population. *J. Occup. Med.* **13**, 256-258.
- Milby, T. H., Samuels, A. J., and Ottoboni, F. (1968). Human exposure to lindane: Blood lindane levels as a function of exposure. *J. Occup. Med.* **10**, 584-587.
- Miller, G. J., and Fox, J. A. (1973). Chlorinated hydrocarbon pesticide residues in Queensland human milks. *Med. J. Aust.* **2**, 261-264.
- Miller, P. E., and Fink, G. B. (1973). Brain serotonin level and pentylenetetrazol seizure threshold in dieldrin and endrin treated mice. *Proc. West. Pharmacol. Soc.* **16**, 195-197.
- Mirakhmedov, U. M., and Karimov, A. M. (1972). The effect of pesticides on the skin of agricultural workers. *Vestn. Dermatol. Venerol.* **46**, 50-52 (in Russian).
- Miranda, C. L., Webb, R. E., and Ritchey, S. J. (1973). Effect of dietary protein quality, phenobarbital and SKF 525-A on heptachlor metabolism in the rat. *Pestic. Biochem. Physiol.* **3**, 456-461.
- Mishra, S. K., Koury, M., and Desai, D. (1980). Inhibition of calcium ATPase activity in rat brain and muscle by chlordane. *Bull. Environ. Contam. Toxicol.* **25**, 262-268.
- Misra, U. K., Nag, D., and Murti, C. R. (1984). A study of cognitive functions in DDT sprayers. *Indian Health* **22**, 199-206.
- Mitjavila, S., Carrera, G., Boigegrain, R.-A., and Derache, R. (1981a). I. Evaluation of the toxic risk of DDT in the rat: During accumulation. *Arch. Environ. Contam. Toxicol.* **10**, 459-469.
- Mitjavila, S., Carrera, G., and Fernandez, Y. (1981b). II. Evaluation of the toxic risk of accumulated DDT in the rat: During fat mobilization. *Arch. Environ. Contam. Toxicol.* **10**, 471-481.
- Miura, K., Ino, T., and Iizuka, M. (1973). Comparison of susceptibility of various strains of mice to acute toxicity of BHC. *Med. Biol.* **86**, 391-396.
- Miura, K., Ino, T., and Iizuka, S. (1974). Comparison of susceptibilities to the acute toxicity of BHC in strains of experimental mice. *Exp. Anim.* **23**, 198 (in Japanese).
- Mizoguchi, M., Yamagishi, T., Ushio, F., Fujimoto, C., Takeba, K., Kani, T., Haruta, M., Yasuhara, K., and Kubota, H. (1972). On the residual amount of organochlorine pesticides in human milk in Tokyo metropolitan area. *Jpn. J. Public Health* **19**, 541-544 (in Japanese).
- Model, A. A. (1968). Peculiarities of neurological symptoms in chronic DDT poisoning. *Sov. Med.* **31**, 110-114 (in Russian).
- Model, A. A., and Larina, M. B. (1957). On BHC poisoning. *Zh. Nevropatol. Psikhiatr. Im. S. S. Korsakova* **57**, 20-21 (in Russian).
- Mohammed, A., Andersson, O., Biessmann, A., and Slanina, P. (1983). Fate and specific tissue retention of toxaphene in mice. *Arch. Toxicol.* **54**, 311-321.
- Mohammed, A., Hallberg, E., Rydström, J., and Slanina, P. (1985). Toxaphene: Accumulation in the adrenal cortex and effect on ACTH-stimulated corticosteroid synthesis in the rat. *Toxicol. Lett.* **24**, 134-143.
- Molnar, G. D., Nunn, S. L., and Tauxe, W. N. (1961). The effect of o,p'-DDD therapy on plasma cholesterol in adrenal carcinoma. *Proc. Staff Meet. Mayo Clin.* **36**, 618-620.
- Molowa, D. T., Wrighton, S. A., Blanke, R. V., and Guzelian, P. S. (1986a). Characterization of a unique aldo-keto reductase responsible for the reduction of chlordane in the liver of the gerbil and man. *J. Toxicol. Environ. Health* **17**, 375-384.
- Molowa, D. T., Shayne, A. G., and Guzelian, P. S. (1986b). Purification and characterization of chlordane reductase from human liver. *J. Biol. Chem.* **261**, 12624-12627.
- Montgomery, J. A., and Struck, R. F. (1973). The relation of the metabolism of anticancer agents to their activity. *Fortschr. Arzneimittelforsch.* **17**, 32-304 (in German).
- Montoya-Cabrera, M. A., de Aquino, Jaso-M. E., Reynoso Garcia, M., Vargas de la Rosa, R., and Hernandez-Zamora, A. (1980). Fatal endrin poisoning. *Bol. Med. Hosp. Infant. Mex. (Span. Ed.)* **37**, 417-423 (in Spanish).
- Moorthy, K. S., Trotman, C. H., Spann, C. H., and Desai, D. (1986). *In vivo* effects of toxaphene on canodulin-regulated calcium-pump activity in rat brain. *J. Toxicol. Environ. Health* **20**, 249-259.
- Morbidity and Mortality Weekly Reports (MMWR) (1981). Chlordane contamination of a public water supply—Pittsburgh, Pennsylvania. *Morbid. Mortal. Wkly. Rep.* **30**, 571-578.
- Morbidity and Mortality Weekly Reports. (MMWR) (1984). Acute convulsions associated with endrin poisoning—Pakistan. *Morbid. Mortal. Wkly. Rep.* **33**, 687-693.
- Morgan, D. P., and Lin, I. L. (1978). Blood organochlorine pesticide concentrations, clinical hematology and biochemistry in workers occupationally exposed to pesticides. *Arch. Environ. Contam. Toxicol.* **7**, 423-447.
- Morgan, D. P., and Roan, C. C. (1969). Renal function in persons occupationally exposed to pesticides. *Arch. Environ. Health* **19**, 633-636.
- Morgan, D. P., and Roan, C. C. (1970). Chlorinated hydrocarbon pesticide residue in human tissues. *Arch. Environ. Health* **20**, 452-457.
- Morgan, D. P., and Roan, C. C. (1971). Absorption, storage, and metabolic conversion of ingested DDT and metabolites in man. *Arch. Environ. Health* **22**, 301-308.
- Morgan, D. P., and Roan, C. C. (1972). Loss of DDT from storage in human body fat. *Nature (London)* **238**, 221-223.
- Morgan, D. P., and Roan, C. C. (1973). Adrenocortical function in persons occupationally exposed to pesticides. *J. Occup. Med.* **15**, 26-28.
- Morgan, D. P., and Roan, C. C. (1974). Liver function in workers having high tissue stores of chlorinated hydrocarbon pesticides. *Arch. Environ. Health* **29**, 14-17.
- Morgan, D. P., and Roan, C. C. (1977). The metabolism of DDT in man. *Essays Toxicol.* **5**, 39.
- Morgan, D. P., Roan, C. C., and Paschal, E. H. (1972). Transport of DDT, DDE and dieldrin in human blood. *Bull. Environ. Contam. Toxicol.* **8**, 321-326.
- Morgan, D. P., Sandifer, S. H., Hetzler, H. L., Slach, E. F., Brady, C. D., and Colclough, J. (1979). Test for *in vivo* conversions of mirex to Kepone. *Bull. Environ. Contam. Toxicol.* **22**, 238-244.
- Morgan, D. P., Roberts, R. J., Walter, A. W., and Stockdale, E. M. (1980). Anemia associated with exposure to lindane. *Arch. Environ. Health* **35**, 307-310.
- Morgan, J. M., and Hickenbottom, J. P. (1979). Comparison of selected parameters for monitoring methoxychlor hepatotoxicity. *Bull. Environ. Contam. Toxicol.* **23**, 275-280.
- Mori, Y., Kikuta, M., Okinaga, E., and Okura, T. (1983). Levels of PCBs and organochlorine pesticides in human adipose tissue collected in Ehime prefecture. *Bull. Environ. Contam. Toxicol.* **30**, 74-79.
- Morita, R., Lieberman, L. M., Beierwaltes, W. H., Conn, J. W., Ansari, A. N., and Nishiyama, H. (1972). Percent uptake of <sup>131</sup>I radioactivity in the adrenal from radioiodinated cholesterol. *J. Clin. Endocrinol. Metab.* **34**, 36-43.
- Morohashi, K., Yoshioka, H., Sogawa, K., Fujii-Kuriyama, Y., and Omura, T. (1984). Induction of mRNA coding for phenobarbital-inducible form of microsomal cytochrome P-450 in rat liver by administration of 1,1-di(p-chlorophenyl)-2,2-dichloroethylene and phenobarbital. *J. Biochem. (Tokyo)* **95**, 949-957.
- Morris, R. D. (1968). Effects of endrin feeding on survival and reproduction in the deer mouse, *Peromyscus maniculatus*. *Can. J. Zool.* **46**, 951-958.
- Moss, J. A., and Hathway, D. E. (1964). Transport of organic compounds in the mammal—partition of dieldrin and Telodrin between the cellular components and soluble proteins of blood. *Biochem. J.* **91**, 384-393.
- Moubry, R. J., Myrdal, G. R., and Sturges, A. (1968). Residues in food and



- feed. Rate of decline of chlorinated hydrocarbon pesticides in dairy milk. *Pestic. Monit. J.* 2, 72-79.
- Mourelle, M., Garcia, M., and Aguilar, C. (1985). Adenosine triphosphatase activities in plasma liver membranes of rats treated with DDT and toxaphene. *J. Appl. Toxicol.* 5, 39-43.
- Mueller, W. F., Nohynek, G., Woods, G., Korte, F., and Coulston, F. (1975a). Comparative metabolism of dieldrin-<sup>14</sup>C in mouse, rat, rabbit, rhesus monkey and chimpanzee. *Chemosphere* 4, 89-92.
- Mueller, W. F., Woods, G., Korte, F., and Coulston, F. (1975b). Metabolism and organ distribution of dieldrin C in rhesus monkeys after single oral and intravenous administration. *Chemosphere* 4, 93-98.
- Mueller, W. F., Iatropoulos, M. J., Rozman, K., Korte, F., and Coulston, F. (1978). Comparative kinetic, metabolic, and histopathologic effects of chlorinated hydrocarbon pesticides in rhesus monkeys. *Toxicol. Appl. Pharmacol.* 45, 283-284.
- Mughal, H. A., and Rahman, A. (1973). Organochlorine pesticide content of human adipose tissue in Karachi. *Arch. Environ. Health* 27, 396-398.
- Muhlen, K. (1946). Significance of dichlor-diphenyl-trichlor methylmethane preparations as an arthropod poison in plagues, with regard to one experience. *Dtsch. Med. Wochenschr.* 71, 164-169 (in German).
- Mukherjee, D., Ghosh, B. N., Chakraborty, J., and Roy, B. R. (1980). Pesticide residues in human tissues in Calcutta. *Indian J. Med. Res.* 72, 583-587.
- Muller, D., Klepel, H., Macholz, R., and Knoll, R. (1981). Electroneurographic and electroencephalographic finding in patients exposed to hexachlorocyclohexane. *Psychiatr. Neurol. Med. Psychol.* 33, 468-472.
- Muminov, A. I. (1972). Functional condition of the hearing organ in persons with pesticide intoxication. *Vestn. Otorinolaringol.* 34, 33-35 (in Russian).
- Munchberg, P. (1949). On the chemistry of impurities of hexachlorocyclohexanes. *Anz. Schaedlingskd.* 22, 116-119.
- Munir, K. M., Soman, C. S., and Bhide, S. V. (1983). Hexachlorocyclohexane-induced tumorigenicity in mice under different experimental conditions. *Tumori* 69, 383-386.
- Munir, K. M., Rao, K. V. K., and Bhide, S. V. (1984). Effect of hexachlorocyclohexane on diethylnitrosamine-induced hepatocarcinogenesis in rat and its failure to promote skin tumors on dimethylbenz[a]anthracene initiation in mouse. *Carcinogenesis (London)* 5, 479-481.
- Munk, Z. M., and Nantel, A. (1977). Acute lindane poisoning with development of muscle necrosis. *Can. Med. Assoc. J.* 117, 1050-1054.
- Munster, A. J., Bollman, H., and Saunders, J. C. (1962). Hexachlorocyclohexane in the treatment of pediculosis. *Arch. Pediatr.* 79, 94-95.
- Murdia, U. K., Munir, K. M., and Bhide, S. V. (1985). Induction of early biochemical events on hexachlorocyclohexane treatment on mouse liver. *Indian J. Biochem. Biophys.* 22, 223-225.
- Murray, C. P. F. V., Saucedo, F. M., and Navarez, G. M. (1973). Environmental contamination and the health of children. *Salud. Publ. Mex.* 15, 91-100 (in Spanish).
- Musial, C. J., Hutzinger, O., Zitko, V., and Crocker, J. (1974). Presence of PCB, DDE and DDT in human milk in the provinces of New Brunswick and Nova Scotia, Canada. *Bull. Environ. Contam. Toxicol.* 12, 258-267.
- Mussalo-Rauhamaa, H., Pyysalo, H., and Moilanen, R. (1984). Influence of diet and other factors on the levels of organochlorine compounds in human adipose tissue in Finland. *J. Toxicol. Environ. Health.* 13, 689-704.
- Mutter, L. C., Blanke, R. V., Jandacek, R. J., and Guzelian, P. S. (1988). Reduction in the body content of DDE in the Mongolian gerbil treated with sucrose polyester and caloric restriction. *Toxicol. Appl. Pharmacol.* 92, 428-435.
- Nadzhimutdinov, K. N., Muzrabekov, S. M., and Kamilov, I. K. (1973). Effect of hexachlorocyclohexane on the action of Hexenal and Corazol. *Med. Zh. Uz.* 4, 54-57 (in Russian).
- Nadzhimutdinov, K. N., Kamilov, I. K., and Muzrabekov, S. M. (1974). Influence of pesticides on the duration of hexobarbital-induced sleep. *Farmakol. Toksikol. (Moscow)* 37, 533-537 (in Russian).
- Naevsted, R. (1947). Poisoning by DDT powder as well as other poisons. *Tidsskr. Nor. Laegeforen.* 67, 261-263 (in Norwegian).
- Nagai, I. (1972). Residues of organochlorine pesticides in mothers' milk in Yamaguchi Prefecture. *Annu. Rep. Yamaguchi Prefect. Res. Inst. Public Health* 14, 93-94 (in Japanese).
- Nagasaki, H. (1973). Experimental studies on chronic toxicity of benzene hexachloride (BHC). *J. Nara Med. Assoc.* 24, 1-26 (in Japanese).
- Nagasaki, H., Tomii, S., Mega, T., Marugami, M., and Ito, N. (1971). Development of hepatomas in mice treated with benzene hexachloride. *Gann* 62, 431.
- Nagasaki, H., Tomii, S., Mega, T., Marugami, M., and Ito, N. (1972a). Hepatocarcinogenic effect of  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -isomers of benzene hexachloride in mice. *Gann* 63, 393.
- Nagasaki, H., Tomii, S., Mega, T., Marugami, M., and Ito, N. (1972b). Carcinogenicity of benzene hexachloride. In "Topics in Chemical Carcinogenesis" (W. Nakahara, ed.), pp. 343-353. University Park Press, Baltimore, Maryland.
- Nagasaki, H., Tomii, S., Tsumashika, T., Marusami, M., Arai, M., and Ito, N. (1972c). On the experimental tumorigenesis of the liver of mice and rats by the induction of BHC isomers,  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ . *Proc. Jpn. Cancer Assoc.* 31, 33.
- Nagasaki, H., Arai, M., Makjura, S., Sugihara, S., Hirao, K., Matsumura, K., and Ito, N. (1973). Studies on interactions of HCB isomers and PCBs in the induction of liver tumors in the mouse. *Collect. Lect. Abstr. United Soc. Cancer Jpn.*, p. 160.
- Nagasaki, H., Aoi, H., Makiura, S., Aoki, Z., Arai, M., Konishi, Y., and Ito, N. (1974). Characteristic features of hepatoma of mice due to  $\alpha$ -BHC and several factors of carcinogenesis. *Proc. Jpn. Cancer Assoc.* 33, 78 (in Japanese).
- Nair, K. K., Bartels, P. H., Mahon, D. C., Olson, G. B., and Oloffs, P. C. (1980). Image analysis of hepatocyte nuclei from chlordane-treated rats. *Anal. Quant. Cytol.* 2, 285-289.
- Nakajima, M. (1983). Biochemical toxicology of lindane and its analogs. *J. Environ. Sci. Health, Part B*, B18, 147-172.
- Narafu, T. (1971). Pollution of cows' milk and human milk by BHC. *J. Clin. Nutr.* 39, 26-34.
- Narayan, S., Bajpai, A., Chauhan, S. S., and Misra, U. K. (1985). Lipid peroxidation in lung and liver of rats given DDT and endosulfan intratracheally. *Bull. Environ. Contam. Toxicol.* 34, 63-67.
- Narbonne, P., and Lièvremon, M. (1983). *In vitro* demonstration of the effect of lindane on isolated synaptosomes preparations. *C. R. Seances Acad. Sci., Ser. 3* 296, 811-814.
- Narloch, B. A., Lawton, M. P., Moody, D. E., Hammock, B. D., and Shull, L. R. (1987). The effects of dicofol on induction of hepatic microsomal metabolism in rats. *Pestic. Biochem. Physiol.* 28, 362-370.
- Naruse, R., Sasaki, T., Yamoka, T., Matsuo, K., Negoro, Y., Itasaka, Y., Urushibata, K., Chin, T., Kaot, K., Kako, K., Goto, Y., Eguchi, Y., Yogo, H., Tomita, A., and Asai, M. (1970). Clinical use of *o,p'*-DDD in adrenal cortex cancer. *Horumon to Rinsho* 18, 241-244 (in Japanese).
- National Cancer Institute (NCI) (1976). "Report on Carcinogenesis Bioassay of Technical Grade Chlordecone (Kepone)." Carcinog. Program, Div. Cancer Cause and Prev., U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1977a). "Bioassay of Lindane for Possible Carcinogenicity," Techn. Rep. Ser. No. 14, DHEW Publ. No. (NIH) 77-814. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1977b). "Bioassay of Chlordane for Possible Carcinogenicity," Techn. Rep. Ser. No. 8, DHEW Publ. No. (NIH) 77-808. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1977c). "Bioassay of Heptachlor for Possible Carcinogenicity," Techn. Rep. Ser. No. 9, DHEW Publ. No. (NIH) 77-809. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978a). "Bioassay of DDT, TDE, and *p,p'*-DDE for Possible Carcinogenicity," Carcinogenesis Tech. Rep. Ser. No. 131, DHEW Publ. No. (NIH) 78-1325. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978b). "Bioassay of Methoxychlor for Possible Carcinogenicity," Techn. Rep. Ser. No. 35, DHEW Publ. No. (NIH) 78-835. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978c). "Bioassay of Chlorobenzilate for Possible Carcinogenicity," Techn. Rep. Ser. No. 75, DHEW Publ. No. (NIH) 78-1325. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978d). "Bioassay of Dicofol for Possible Carcinogenicity," Techn. Rep. Ser. No. 90, DHEW Publ. No. (NIH) 78-1340. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978e). "Bioassay of Aldrin and Dieldrin for Possible Carcinogenicity," Techn. Rep. Ser. No. 21, DHEW Publ. No. (NIH) 78-821. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978f). "Bioassay of Endosulfan for Possible Carcinogenicity in Rats," Carcinogenesis Tech. Rep. Ser. No. 22, DHEW Publ. No. (NIH) 78-822. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1978g). "Bioassay of *p,p'*-Ethyl-DDD for Possible Carcinogenicity," Carcinogenesis Tech. Rep. Ser. No. 22, DHEW Publ. No. (NIH) 78-822. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1979a). "Bioassay of *p,p'*-Ethyl-DDD for Possible Carcinogenicity," Carcinogenesis Tech. Rep. Ser. No. 22, DHEW Publ. No. (NIH) 79-1712. U.S. Govt. Printing Office, Washington, D.C.
- National Cancer Institute (NCI) (1979b). "Bioassay of Toxaphene for Possible Carcinogenicity," Carcinogenesis Tech. Rep. Ser. No. 37, DHEW Publ. No. (NIH) 79-837. U.S. Govt. Printing Office, Washington, D.C.
- Nawa, H. (1973). Studies on intoxication by organochlorine pesticides for agricultural use. Part 2. Examination of concentration of organochlorine pesticides in sera of healthy people and of patients with various diseases. *J. Okayama Med. Soc.* 85, 47-58 (in Japanese).
- Nayshteyn, S. Y., and Leybovich, D. L. (1971). Low doses of DDT,  $\gamma$ -HCH and mixtures of these: Effect on sexual function and embryogenesis in rats. *Gig. Sanit.* 36, 19-22 (in Russian).
- Neal, P. A., von Oettingen, W. F., Smith, W. W., Malmo, R. B., Dunn, R. C., Moran, H. E., Sweeney, T. R., Armstrong, D. W., and White, W. C. (1944). Toxicity and potential dangers of aerosols, mists, and dusting powders containing DDT. *Public Health Rep. Suppl.* 177, 1-32.
- Neal, P. A., Sweeney, T. R., Spicer, S. S., and von Oettingen, W. F. (1946). The excretion of DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane) in man, together with clinical observations. *Public Health Rep.* 61, 403-409.
- Nelson, A. A., and Woodard, G. (1948). Adrenal cortical atrophy and liver damage produced in dogs by feeding 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane (DDD). *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 7, 277.
- Nelson, A. A., and Woodard, G. (1949). Severe adrenal cortical atrophy (cytotoxic and hepatic damage produced in dogs by feeding 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane (DDD or TDE). *Arch. Pathol.* 48, 387-394.
- Nelson, A. A., Draize, J. H., Woodard, G., Fitzhugh, O. G., Smith, R. B., Jr., and Calvery, H. O. (1944). Histopathological changes following administration of DDT in several species of animals. *Public Health Rep.* 59, 1009-1020.
- Nelson, E. (1953). Aldrin poisoning. *Rocky Mt. Med. J.* 50, 483-486.
- Nelson, J. A. (1973). Effects of DDT analogs and polychlorinated biphenyls (PCB) mixtures on <sup>3</sup>H-estradiol binding to rat uterine receptor. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 32, 236.
- Nelson, J. O., and Matsumura, F. (1975). A simplified approach to studies of toxic toxaphene components. *Bull. Environ. Contam. Toxicol.* 13, 464-470.
- Newman, S. L., and Guzelian, P. S. (1983). Identification of the cyanopregnenolone-inducible form of hepatic cytochrome P-450 as a catalyst of aldrin epoxidation. *Biochem. Pharmacol.* 32, 1529-1531.
- Newton, K. G., and Greene, N. C. (1972). Organochlorine pesticide residue levels in human milk—Victoria, Australia—1970. *Pestic. Monit. J.* 6, 4-8.
- Nicholls, R. W. (1958). A case of acute poisoning by BHC. *Med. J. Aust.* 1, 42-43.
- Nichols, J., Kaye, S., and Larson, P. S. (1958). Barbiturate potentiating action of DDD and Perthane. *Proc. Soc. Exp. Biol. Med.* 98, 239-242.
- Nichols, J., Prestley, W. E., and Nichols, F. (1961). Effects of *m,p'*-DDT in a case of adrenal cortical carcinoma. *Curr. Ther. Res.* 3, 266-271.
- Nigam, S. K., Lakkad, B. C., Karnik, A. B., Thakore, K. N., Bhatt, D. K., Aravindra Babu, K., and Kashyap, S. K. (1979). Effect of hexachlorocyclohexane feeding on testicular tissue of pure inbred Swiss mice. *Bull. Environ. Contam. Toxicol.* 23, 431-437.
- Nigam, S. K., Bhatt, D. K., Karnik, A. B., Thakore, K. N., Babu, K. A., Lakkad, B. C., Kashyap, S. K., and Chatterjee, S. K. (1981). Experimental studies on insecticides commonly used in India. *J. Cancer Res. Clin. Oncol.* 99, 143-152.
- Nigam, S. K., Thakore, K. N., Karnik, A. B., and Lakkad, B. C. (1984). Hepatic glycogen, iron distribution and histopathological alterations in mice exposed to hexachlorocyclohexane. *Indian J. Med. Res.* 79, 571-579.
- Nigam, S. K., Karnik, A. B., Majumder, S. K., Visweswariah, K., Suryanarayana Raju, G., Muktha Bai, K., Lakkad, B. C., Thakore, K. N., and Chatterjee, B. B. (1986). Serum hexachlorocyclohexane residues in workers engaged at a HCH manufacturing plant. *Int. Arch. Occup. Environ. Health* 57, 315-320.
- Nigg, H. N., Stamper, J. H., and Queen, R. M. (1986). Dicofol exposure to Florida citrus applicators: Effects of protective clothing. *Arch. Environ. Contam. Toxicol.* 15, 121-134.
- Nikitina, Y. I. (1974). Course of labor and puerperium in vineyard workers and milkmaids in the Crimea. *Gig. Tr. Prof. Zabol.* 18, 17-20 (in Russian).
- Nikolayev, A. I., and Usmanova, I. Y. (1971). Production of antibodies to pesticides. *Lab. Delo* 11, 676-678 (in Russian).
- Nishimoto, T., Uyeta, M., and Taue, S. (1970). The accumulation of organochlorine pesticides in human adipose tissue. *Prog. Med.* 73, 275-277.
- Nitsche, K., Lange, M., Bauer, E., and Zesch, A. (1984). Quantitative distribution of locally applied lindane in human skin and subcutaneous fat *in vitro*. Dependence of penetration on the applied concentration, skin state, duration of action and nature and time of washing. *Dermatosen. Beruf. Umwelt* 32, 161-165 (in German).
- Nitschke, U., and Link, K. (1972). Clinical and biochemical aspects of hormone-producing adrenal carcinomas. *Z. Gesamte Inn. Med. Ihre Grenzgeb.* 27, 896-905 (in German).
- Noack, G., and Portig, J. (1973). Biodegradation of alpha-hexachlorocyclohexane. III. Decrease in liver non-protein thiol after intragastric application of the drug. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 280, 183-189.
- Noda, K., Hirabayashi, M., Yonemura, I., Maruyama, M., and Endo, I. (1972). Influence of pesticides on embryos. II. On the influence of organochlorine pesticides. *Pharmacometrics* 6, 673-679.
- North, H. H., and Menzer, R. E. (1973). Metabolism of DDT in human embryonic lung cell cultures. *J. Agric. Food Chem.* 21, 509-510.
- Nowak, W., Lotocki, W., Szredzinski, J., Stasiewicz, A., and Badurski, J. (1971). Dieldrin poisoning during pregnancy. *Pol. Tyg. Lek.* 25, 958-959 (in Polish).
- Oberholser, K. M., Wagner, S. R., and Greene, F. E. (1977). Factors affecting dieldrin metabolism by rat liver microsomes. *Drug. Metab. Dispos.* 5, 302-309.
- Obuchowska, D., and Pawlowska-Tochman, A. (1973). The effect of the gamma-isomer of HCH (lindane) on the ultrastructure of the liver cell. *Medicine (Baltimore)* 28, 63-66.
- Odler, M. (1973). The effect of some chlorinated insecticides on the activity of chorionic gonadotrophin in rats. *Comp. Gen. Pharmacol.* 4, 293-295.
- Oesch, F., Freidberg, T., Herbst, M., Paul, W., Wilhelm, N., and Bentley, P. (1982). Effects of lindane treatment on drug metabolizing enzymes and liver weight of CF1 mice in which it evoked hepatomas and in non-susceptible rodents. *Chem.-Biol. Interact.* 40, 1-14.
- Offner, H., Konat, G., and Clausen, J. (1973). The effect of DDT, lindane and Aroclor 1254 on brain cell culture. *Environ. Physiol. Biochem.* 3, 204-211.
- Ofner, R. R., and Calvery, H. O. (1945). Determination of DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane) and its metabolite in biological materials by use of the Schecter-Haller method. *J. Pharmacol. Exp. Ther.* 85, 363-370.
- Ogata, N., Vogel, S. M., and Narahashi, T. (1988). Lindane but not deltamethrin blocks a component of GABA-activated chloride channels. *FASEB J.* 2, 2895-2900.



- Ohno, Y., Kawanishi, T., Takahashi, A., Nakaura, S., Kawashima, K., Tanaka, S., Takanaka, A., Omori, Y., Sekita, H., and Uchiyama, M. (1986). *J. Toxicol. Sci.* **11**, 111-123.
- Ohsawa, T., Knox, J. R., Khalifa, S., and Casida, J. E. (1975). Metabolic dechlorination of toxaphene in rats. *J. Agric. Food Chem.* **23**, 98-106.
- Ohyama, T., Takahashi, T., and Ogawa, H. (1982). Effects of dichlorodiphenyltrichloroethane and its analogues on rat liver mitochondria. *Biochem. Pharmacol.* **31**, 397-404.
- Ojima, M., Saito, M., and Fukushima, S. (1984). Effect of an insecticide (*o,p'*-DDD) on human adrenal synthesis. *Nippon Naibunpi Gakkai Zasshi* **60**, 852-871 (in Japanese).
- Ojima, M., Saitoh, M., Itoh, N., Kusano, Y., Fukuchi, S., and Naganuma, H. (1985). Effect of *o,p'*-DDD on adrenal steroidogenesis and hepatic steroid metabolism. *Nippon Naibunpi Gakkai Zasshi* **61**, 168-178 (in Japanese).
- Olanoff, L. S., Bristow, W. J., Colcolough, J., and Reigart, J. R. (1983). Acute chlordane intoxication. *J. Toxicol. Clin. Toxicol.* **20**, 291-306.
- O'Leary, J. A., Davies, J. E., and Feldman, M. (1970). Spontaneous abortion and human pesticide residues of DDT and DDE. *Am. J. Obstet. Gynecol.* **108**, 1291-1292.
- Olson, K. L., Matsumura, F., and Boush, G. M. (1980). Behavioural effects on juvenile rats from perinatal exposure to low levels of toxaphene, and its toxic components: toxicant A, and toxicant B. *Arch. Environ. Contam. Toxicol.* **9**, 247-257.
- Olszyna-Marzys, A. E., de Campos, M., Farvar, M. T., and Thomas, M. (1973). Residues of chlorinated pesticides in human milk in Guatemala. *Bol. Of. Sanit. Panam.* **74**, 93-107 (in Spanish).
- Omirov, P. Y., and Talan, K. A. (1970). Rabbit autoimmunization under conditions of chronic poisoning with hexachlorane (BHC) and methyl mercaptophos. *Med. Zh. Uz.* **7**, 11-12 (in Russian).
- Onifer, T. M., and Whisnant, J. P. (1957). Cerebellar ataxia and neuronitis after exposure to DDT and lindane. *Proc. Staff Meet. Mayo Clin.* **32**, 67-72.
- Orr, J. W. (1948). Absence of carcinogenic activity of benzene hexachloride ("Gammexane"). *Nature (London)* **162**, 189.
- Ortega, P. (1966). Light and electron microscopy of dichlorodiphenyltrichloroethane (DDT) poisoning in the rat liver. *Lab. Invest.* **15**, 657-679.
- Ortega, P., Hayes, W. J., Jr., Durham, W. F., and Mattson, A. (1956). "DDT in the Diet of the Rat," Public Health Monogr. No. 43, Public Health Serv. Publ. No. 484. U.S. Govt. Printing Office, Washington, D.C.
- Ortega, P., Hayes, W. J., Jr., and Durham, W. F. (1957). Pathologic changes in the liver of rats after feeding low levels of various insecticides. *Arch. Pathol.* **64**, 614-622.
- Ortelee, M. F. (1958). Study of men with prolonged intensive occupational exposure to DDT. *Arch. Ind. Health* **18**, 433-440.
- Oshiba, K. (1972). Experimental studies on the fate of  $\beta$ - and  $\gamma$ -BHC in vivo following daily administration. *J. Osaka City Med. Cent.* **21**, 1-9 (in Japanese).
- Oshiba, K., and Fujita, T. (1974). Interaction between toxicant and nutrition. Part 7. Effects of dietary protein levels on the  $\beta$ -BHC deposition in dam and offspring of rats during gestation and lactation. *J. Food Hyg. Soc. Jpn.* **15**, 342-348 (in Japanese).
- Oshiba, K., and Kawakita, H. (1970). Interaction between toxicant and nutrition. II. Relationship between concentrations of  $\gamma$ -BHC in diet and deposition of the chemical in animal tissues. *J. Food Hyg. Soc. Jpn.* **11**, 445-448 (in Japanese).
- Oshiba, K., and Kawakita, H. (1971). The relationship between toxic substances and nutrition. Part 5. Effects of dietary protein and fat starvation on excretion of accumulated BHC. *Rep. Osaka Munic. Inst. Public Health* **34**, 158 (in Japanese).
- Oshiba, K., and Kawakita, H. (1972a). Interaction between toxicants and nutrition. III. Distribution and deposition of  $\beta$ -BHC in rat tissues. *J. Food Hyg. Soc. Jpn.* **13**, 184-188 (in Japanese).
- Oshiba, K., and Kawakita, H. (1972b). Interaction between toxicants and nutrition. IV. Effect of lipid metabolism on reduction of BHC deposition in rat tissues. *J. Food Hyg. Soc. Jpn.* **13**, 189-194 (in Japanese).
- Oshiba, K., and Kawakita, H. (1972c). Relationship between toxic substances and nutrition. VI. Absorption and excretion of benzene hexachloride. *J. Food Hyg. Soc. Jpn.* **13**, 244-245 (in Japanese).
- Oshiba, K., and Kawakita, H. (1972d). Interaction between toxicant and nutrition. V. The fate of  $\beta$ - and  $\gamma$ -BHC in vivo following dietary protein levels. *J. Food Hyg. Soc. Jpn.* **13**, 383-387 (in Japanese).
- Oshiba, K., and Kawakita, H. (1973). Interactions between toxicants and nutrition. Part 6. Studies on absorption and excretion of BHC in rats. *J. Food Hyg. Soc. Jpn.* **14**, 452-456 (in Japanese).
- Osuntokun, B. O. (1964). "Gammelin 20" poisoning: A report of two cases. *West Afr. Med. J.* **13**, 207-210.
- Ottoboni, A. (1969). Effect of DDT on reproduction in the rat. *Toxicol. Appl. Pharmacol.* **14**, 74-81.
- Ottoboni, A. (1972). Effect of DDT on the reproductive lifespan in the female rat. *Toxicol. Appl. Pharmacol.* **22**, 497-502.
- Ottoboni, A., Bissell, G. D., and Hexter, A. C. (1977). Effects of DDT on reproduction in multiple generations of beagle dogs. *Arch. Environ. Contam. Toxicol.* **6**, 83-101.
- Ottolenghi, A. D., Haseman, J. K., and Suggs, F. (1974). Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. *Teratology* **9**, 11-16.
- Oura, H., Kobayashi, H., Oura, T., Senda, I., and Kubota, K. (1972). On the pollution of human milk by PCB and organochlorine pesticides. *J. Jpn. Assoc. Rural Med.* **21**, 300-301 (in Japanese).
- Ousterhaut, J., Struck, R. F., and Nelson, J. A. (1981). Estrogenic activities of methoxychlor metabolites. *Biochem. Pharmacol.* **30**, 2869-2871.
- Ouw, K. H., and Shandar, A. G. (1974). A health survey of Wee Waa residents during 1973 aerial spraying season. *Med. J. Aust.* **2**, 871-873.
- Paccagnella, B., Prati, L., and Cavazzini, G. (1967). Organochlorine insecticides in the adipose tissue of persons living in the province of Ferrara. *Nuovi Ann. Ig. Microbiol.* **18**, 17-26 (in Italian).
- Palin, K. J., Wilson, C. G., Davis, S. S., and Phillips, A. J. (1982). The effects of oils on the lymphatic absorption of DDT. *J. Pharm. Pharmacol.* **34**, 707-710.
- Pall, H. S., Williams, A. C., Waring, R., and Elias, E. (1987). Motoneurone disease as manifestation of pesticide toxicity. *Lancet* **2**, 685.
- Palmer, K. A., Green, S., and Legator, M. S. (1972). Cytogenic effects of DDT and derivatives of DDT in a cultured mammalian cell line. *Toxicol. Appl. Pharmacol.* **22**, 355-364.
- Paludan, J. (1959). Poisoning with gamma-hexachlorocyclohexane. *Ugeskr. Laeg.* **121**, 2023-2028 (in Danish).
- Panjia, R. K., and Choudhury, S. (1969). A clinical trial with gamma benzene hexachloride in scabies. *Indian J. Dermatol.* **14**, 136-137.
- Paramonchik, V. M. (1966). State of the protein forming function of the liver in persons working with chlororganic chemical poisons. *Vrach. Delo* **11**, 85-88 (in Russian).
- Paramonchik, V. M., and Platonova, V. I. (1968). The functional state of the liver and stomach in persons exposed to the action of organochlorine chemical poisons. *Gig. Tr. Prof. Zabol.* **12**, 27-31 (in Russian).
- Pardini, R. S., Heidker, J. C., and Payne, B. (1971). The effect of some cyclodiene pesticides, benzenehexachloride and toxaphene on mitochondrial electron transport. *Bull. Environ. Contam. Toxicol.* **6**, 436-444.
- Park, K. S., and Bruce, W. N. (1968). The determination of the water solubility of aldrin, dieldrin, heptachlor, and heptachlor epoxide. *J. Econ. Entomol.* **61**, 770-774.
- Parlar, H., Nitz, S., Gäh, S., and Korte, F. (1977). A contribution to the structure of the toxaphene components. Spectroscopic studies on chlorinated bornane derivatives. *J. Agric. Food Chem.* **25**, 68-72.
- Parries, G. S., and Hokin-Neaverson, M. (1985). Inhibition of phosphatidylinositol synthase and other membrane-associated enzymes by stereoisomers of hexachlorocyclohexane. *J. Biol. Chem.* **260**, 2687-2693.
- Paschal, E. H., Roan, C. C., and Morgan, D. P. (1974). Evidence of excretion of chlorinated hydrocarbon pesticides by the human liver. *Bull. Environ. Contam. Toxicol.* **12**, 547-554.
- Patel, T. B., and Rao, V. N. (1958). Dieldrin poisoning in man. A report of 20 cases in Bombay State. *Br. Med. J.* **1**, 919-921.
- Paul, A. H. (1959). Dieldrin poisoning. *N. Z. Med. J.* **58**, 393.
- Peakall, D. B. (1976). Effects of toxaphene on hepatic enzyme induction and circulating steroid levels in the rat. *Environ. Health Perspect.* **13**, 117-120.
- Pearce, G. W., Mattson, A. M., and Hayes, W. J., Jr. (1952). Examination of human fat for presence of DDT. *Science* **116**, 254-256.
- Pearl, W., and Kupfer, D. (1972). Stimulation of dieldrin elimination by a thiouracil derivative and DDT in the rat: Enhancement of dieldrin oxidative metabolism? *Chem.-Biol. Interact.* **4**, 91-96.
- Peck, A. W. (1970). Impotence in farm workers. *Br. Med. J.* **1**, 690.
- Peeler, D. F. (1976). Open field activity as a function of preweaning or generational exposure to mirex. *J. Miss. Acad. Sci.* **21**, 58.
- Péllissier, M. A., Manchon, P., Atteba, S., and Albrecht, R. (1975). Some effects of treatment with lindane on the microsomal enzymes of rat liver. *Food Cosmet. Toxicol.* **13**, 437-440 (in French).
- Pellerin, D., Harouchi, A., and Soulier, Y. (1975). Corticoadrenal tumors concerning 10 cases. *Ann. Chir. Infant.* **16**, 155-179 (in French).
- Pepprell, J. (1981). The induction of hepatic microsomal mixed-function oxidase activities in the mouse by mirex, 3,4,5,3',4',5'-hexachlorobiphenyl, and equimolar dosages of both. *Environ. Res.* **26**, 402-408.
- Peraino, C., Fry, R. J. M., Staffeldt, E., and Christopher, J. P. (1975). Comparative enhancing effects of phenobarbital, amobarbital, diphenylhydantoin, and dichlorodiphenyltrichloroethane on 2-acetylaminofluorene-induced hepatic tumorigenesis in the rat. *Cancer Res.* **35**, 2884-2890.
- Pereira, M. A., Herren, S. L., Britt, A. L., and Khoury, M. M. (1982). Sex difference in enhancement of GGTase-positive foci by hexachlorobenzene and lindane in rat liver. *Cancer Lett.* **15**, 95-101.
- Perevodchikova, N. I., Platinskiy, L. V., and Kerstman, V. I. (1972). The treatment of inoperable forms of malignant tumors of the adrenal cortex with *o,p'*-DDD. *Vopr. Onkol.* **18**, 24-29 (in Russian).
- Pernov, K., and Kyurkchiye, S. (1974). Acute occupational poisoning by lindane. *Gig. Tr. Prof. Zabol.* **12**, 46-47 (in Russian).
- Pesendorfer, H. (1975). Organochlorine pesticide (DDT, etc.) and polychlorinated biphenyl (PCB) compound residues in human milk (from the area of Vienna and lower Austria). *Wien. Klin. Wochenschr.* **87**, 732-736 (in German).
- Pesendorfer, H., Eichler, I., and Glofke, E. (1973). Informative analyses of organochlorine pesticide and PCB residues in human adipose tissue (from the area of Vienna). *Wien. Klin. Wochenschr.* **85**, 218-222 (in German).
- Peterson, J. E., and Robinson, W. H. (1964). Metabolic products of *p,p'*-DDT in the rat. *Toxicol. Appl. Pharmacol.* **6**, 321-327.
- Peto, R. (1980). Distorting the epidemiology of cancer: The need for a more balanced overview. *Nature (London)* **284**, 297-300.
- Petrella, V. J., Fox, J. P., and Webb, R. E. (1975). Endrin metabolism in endrin-susceptible and -resistant strains of pine mice. *Toxicol. Appl. Pharmacol.* **34**, 283-291.
- Petrin, N. M., and Nikulina, G. G. (1970). The effect of chronic administration of different doses of *o,p'*-DDD on the ratio of ascorbic and dehydroascorbic acid in the adrenals and some other organs of guinea-pigs. *Vopr. Endokrinol. Obmena Veshchestv* **1**, 19-22 (in Russian).
- Pfeilsticker, K. (1973). Pesticides in baby food. *Monatsschr. Kinderheilkd.* **121**, 551-553 (in German).
- Phillips, F. S., and Gilman, A. (1946). Studies on the pharmacology of DDT (2,2-bis-(parachlorophenyl)-1,1,1-trichloroethane). I. The acute toxicity of DDT following intravenous injection in mammals with observations on the treatment of acute DDT poisoning. *J. Pharmacol. Exp. Ther.* **86**, 213-221.
- Phillips, F. S., Gilman, A., and Crescitelli, F. N. (1946). Studies on the pharmacology of DDT (2,2-bis-(parachlorophenyl)-1,1,1-trichloroethane). II. The sensitization of the myocardium to sympathetic stimulation during acute DDT intoxication. *J. Pharmacol. Exp. Ther.* **86**, 222-228.
- Phillips, D. E., and Eroschenko, V. P. (1982). An electron microscopic study of chlordecone (Kepone) induced peripheral nerve damage in adult mice. *Neurotoxicology* **3** (2), 155-162.
- Phillips, D. E., and Eroschenko, V. P. (1985a). An electron microscopic study of alterations in mouse peripheral nerve and skeletal muscle after chlordecone exposure. *Neurotoxicology* **6** (1), 141-150.
- Phillips, D. E., and Eroschenko, V. P. (1985b). Effect of the insecticide chlordecone on the ultrastructure of mouse skeletal muscle. *Neurotoxicology* **6**, (3), 45-52.
- Phokas, E., Andriotakis, K. N., and Kaklamanis, P. M. (1960). On two cases of poisoning by aldrin. *Hellen. Iatr.* **29**, 910-916 (in Greek).
- Pick, I. A., Josha, H., Leffkowitz, M., and Gutman, A. (1965). Aplastic anemia following exposure to aldrin. *Harefuah* **68**, 164-167 (in Hebrew).
- Pietsch, R. L., Finklea, J. F., and Ecotr, W. L. (1969). Stolen pesticides. *J. S. C. Med. Assoc.* **65**, 237-238.
- Pines, A., Cucos, S., Pnina, E., and Ron, M. (1987). Some organochlorine insecticide and polychlorinated biphenyl blood residues in infertile males in the general Israeli population of the middle 1980's. *Arch. Environ. Contam. Toxicol.* **16**, 587-597.
- Pittman, K. A., Kennedy, M. W., and Treble, D. H. (1975). Mirex kinetics in the rhesus monkey. *Toxicol. Appl. Pharmacol.* **33**, 196-197.
- Pittman, K. A., Wiener, M., and Treble, D. H. (1976). Mirex kinetics in the rhesus monkey. II. Pharmacokinetic model. *Drug. Metab. Dispos.* **4**, 288-295.
- Pittz, E. P., Rourke, D., Abraham, R., and Coulston, F. (1979). Alterations in hepatic microsomal proteins of mice administered mirex orally. *Bull. Environ. Contam. Toxicol.* **21**, 344-351.
- Plaa, G. L., Caille, G., Vezina, M., Moritake, I., and Cote, M. G. (1987). Chloroform interaction with chlordecone and mirex: Correlation between biochemical and histological indexes of toxicity and quantitative tissue levels. *Fundam. Appl. Toxicol.* **9**, 198-207.
- Planche, G., Croisy, A., Malaveille, C., Tomatis, L., and Bartsch, H. (1979). Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethyl acetate (Kelthane acetate) as mutagens in *Salmonella typhimurium* and of 1,1-bis(*p*-chlorophenyl) ethylene oxide, a likely metabolite, as an alkylating agent. *Chem.-Biol. Interact.* **25**, 157-175.
- Platonova, V. I. (1970). Disturbances of the functional conditions of the stomach with the prolonged effect on the body of some organochlorine pesticides. *Gig. Tr.* **6**, 142-147 (in Russian).
- Pocock, D. E., and Vost, A. (1974). DDT absorption and chylomicron transport in rat. *Lipids* **9**, 374-381.
- Podowski, A. A., Banerjee, B. C., Feroz, M., Dudek, M. A., Willey, R. C., and Khan, M. A. Q. (1979). Photolysis of heptachlor and *cis*-chlordane and toxicity of their photoisomers to animals. *Arch. Environ. Contam. Toxicol.* **8**, 509-518.
- Pohland, R. C., and Counsell, R. E. (1985). *In vitro* and *in vivo* metabolism of a radiolabeled analog of 1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane. *Drug. Metab. Dispos.* **13**, 113-115.
- Poland, A., Smith, D., Kuntzman, R., Jacobson, M., and Conney, A. H. (1970). Effect of intensive occupational exposure to DDT on phenylbutazone and cortisol metabolism in human subjects. *Clin. Pharmacol. Ther.* **11**, 724-732.
- Polishuk, Z. W., Wasserman, M., Wasserman, D., Groner, Y., Luzarovici, S., and Tomatis, L. (1970). Effects of pregnancy on storage of organochlorine insecticides. *Arch. Environ. Health* **20**, 215-217.
- Polishuk, Z. W., Ron, M., Wassermann, M., Cucos, S., Wassermann, D., and Lemesch, C. (1977). Organochlorine compounds in human blood plasma and milk. *Pestic. Monit. J.* **10**, 121-129.
- Pollock, G. A., and Kilgore, W. W. (1980a). Toxicities and descriptions of some toxaphene fractions: Isolation and identification of a highly toxic component. *J. Toxicol. Environ. Health* **6**, 115-125.
- Pollock, G. A., and Kilgore, W. W. (1980b). Excretion and storage of [<sup>14</sup>C]toxaphene and two isolated [<sup>14</sup>C]toxaphene fractions. *J. Toxicol. Environ. Health* **6**, 127-140.
- Pollock, R. W. (1953). Toxaphene poisoning—report of a fatal case. *Northwest Med.* **52**, 293-294.
- Pollock, R. W. (1958). Toxaphene—lindane poisoning by cutaneous absorption: Report of a case with recovery. *Northwest Med.* **57**, 325-326.
- Polyak, N. R. (1974). Immunoserological and immunocytological reactions in response to sensitization with some pesticides. *Gig. Tr. Prof. Zabol.* **5**, 14-17 (in Russian).



- Popp, J. A., Scortichini, B. H., and Garvey, L. K. (1985). Quantitative evaluation of hepatic foci of cellular alteration occurring spontaneously in Fischer-344 rats. *Fundam. Appl. Toxicol.* **5**, 314-319.
- Portig, J., Kraus, P., Sodomann, S., and Noack, G. (1973). Biodegradation of alpha-hexachlorohexane. I. Glutathione-dependent conversion to a hydrophilic metabolite by rat liver cytosol. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **279**, 185-198.
- Portig, J., Kraus, P., Stein, K., Koransky, W., Noack, G., Gross, B., and Sodomann, S. (1979). Glutathione conjugate formation from hexachlorocyclohexane and pentachlorocyclohexane by rat liver *in vitro*. *Xenobiotica* **9**, 353-378.
- Pott, P. (1975). "Chirurgical Observations Relative to the Cataract, the Prolapsus of the Nose, the Cancer of the Scrotum, etc." T. F. Carnegie, London.
- Pott, P. (1790). "The Chirurgical Works of Percival Pott, FRS, Surgeon to St. Bartholomew's Hospital, A New Edition with his Last Corrections." L. Johnson, London.
- Powell, G. M. (1980). Toxicity of lindane. *Cent. Afr. J. Med.* **26**, 170.
- Powers, J. M., Hennigar, G. R., Grooms, G., and Nichols, J. (1974). Adrenal cortical degeneration and regeneration following administration of DDT. *Am. J. Pathol.* **75**, 181-194.
- Pozo Lora, R., Martache, A. H., Villar, L. M. P., Gimenez, R. L., Villarejo, M. J., and Perez, J. I. (1979). Plaquidosis organoclorados en leches humanas españolas. *Rev. Esp. Pediatr.* **35**, 93-110 (in Spanish).
- Pramanik, A. K., and Hansen, R. C. (1979). Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch. Dermatol.* **15**, 1224-1225.
- Prasad Rao, K. S., Trotman, C. H., Morrow, W., and Desai, D. (1986). Toxaphene inhibition of calmodulin dependent calcium ATPase in rat brain synaptosomes. *Fundam. Appl. Toxicol.* **6**, 642-653.
- Prati, L., and Del Dot, M. (1971). Studies on synthetic organochlorine pesticide accumulation levels in human adipose tissues in the province of Trento. *Ig. Mod.* **64**, 36-44 (in Italian).
- Preston, R. J., Au, W., Bender, M. A., Brewen, J. G., Carrano, A. V., Heddle, J. A., McFee, A. F., Wolff, S., and Wassom, J. S. (1981). Mammalian *in vivo* and *in vitro* cytogenic assays: A report of the U.S. EPA Gene-Tox Program. *Mutat. Res.* **87**, 143-188.
- Princi, F. (1954). Toxicity of the chlorinated hydrocarbon insecticides. *Atti Congr. Int. Med. Lav.*, 11th, pp. 253-272 (in Italian).
- Princi, F., and Spurbeck, G. H. (1951). A study of workers exposed to insecticides chlordan, aldrin, dieldrin. *Arch. Ind. Hyg. Occup. Med.* **3**, 64-72.
- Prior, P. F., and Deacon, P. A. (1969). Spontaneous sleep in healthy subjects in long-term serial electroencephalographic recordings. *Electroencephalogr. Clin. Neurophysiol.* **27**, 422-424.
- Procianny, R. S., and Schwartzman, S. (1982). Serum DDT levels in a non-occupationally exposed pediatric population (São Paulo, Brazil). *J. Trop. Pediatr.* **28**, 308-309.
- Probst, G. S., McMahon, R. E., Hill, L. E., Thompson, C. Z., Epp, J. K., and Neal, S. B. (1981). Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. *Environ. Mutat.* **3**, 11-32.
- Purres, J. (1982). Safety of gamma benzene hexachloride. *J. Am. Acad. Dermatol.* **7**, 407-408.
- Quinby, G. E., Hayes, W. J., Jr., Armstrong, J. F., and Durham, W. F. (1965a). DDT storage in the US population. *JAMA, J. Am. Med. Assoc.* **191**, 109-113.
- Quinby, G. E., Armstrong, J. F., and Durham, W. F. (1965b). DDT in human milk. *Nature (London)* **207**, 726-728.
- Rabello, M. N., Becak, W., Almeida, W. F., Pigati, P., Ungaro, M. T., Murata, T., and Pereira, C. A. B. (1975). Cytogenic study on individuals occupationally exposed to DDT. *Mutat. Res.* **28**, 449-454.
- Radeleff, R. D. (1964). "Veterinary Toxicology." Lea & Febiger, Philadelphia, Pennsylvania.
- Radeleff, R. D., Woodard, G. T., Nickerson, W. J., and Bushland, R. C. (1955). The acute toxicity of chlorinated hydrocarbon and organic phosphorus insecticides to livestock. *U.S., Dep. Agric., Tech. Bull.* **1122**.
- Radomski, J. L., Deichmann, W. B., MacDonald, W. E., and Glass, E. M. (1965). Synergism among oral carcinogens. I. Results of simultaneous feeding of four tumorigens to rats. *Toxicol. Appl. Pharmacol.* **7**, 652-656.
- Radomski, J. L., Deichmann, W. B., and Clizer, E. E. (1968). Pesticide concentrations in the liver, brain, and adipose tissue of terminal hospital patients. *Food Cosmet. Toxicol.* **6**, 209-220.
- Radomski, J. L., Astolfi, E., Deichmann, W. B., and Rey, A. A. (1971). Blood levels of organochlorine pesticides in Argentina: Occupationally and nonoccupationally exposed adults, children, and newborn infants. *Toxicol. Appl. Pharmacol.* **20**, 186-193.
- Rahman, J., Singh, M. V., and Datia, S. P. (1958). Toxicity of dieldrin to human beings. *Bull. Natl. Soc. Ind. Mal. Mosq. Dis.* **6**, 107-111.
- Raizada, R. B., Misra, P., Saxena, I., Datta, K. K., and Dikshith, T. S. S. (1980). Weak estrogenic activity of lindane in rats. *J. Toxicol. Environ. Health* **6**, 483-492.
- Raloff, J. (1976). The Kepone episode. *Chemistry* **49**, 20-21.
- Ramachandran, M., Sharma, M. I. D., Sharma, S. C., Mathur, P. S., Aravindakshan, A., and Edward, G. J. (1973). DDT and its metabolites in human body fat in India. *Bull. W.H.O.* **49**, 637-638.
- Ramachandran, M., Zaidi, S. A., Banerjee, B. D., and Hussain, Q. Z. (1984). Urinary excretion of DDA: 2,2-bis(4-chlorophenyl) acetic acid as an index of DDT exposure in men. *Indian J. Med. Res.* **80**, 483-486.
- Ramakrishnan, N., Kaphalia, B. S., Seth, T. D., and Roy, N. K. (1985). Organochlorine pesticide residues in mother's milk: A source of toxic chemicals in suckling infants. *Hum. Toxicol.* **4**, 7-12.
- Ramakrishnan, S., Srinivasan, V., and Nedugadi, T. M. B. (1961). Effect of gammexane on flavoprotein enzymes of rat liver. *Curr. Sci.* **30**, 416-417.
- Ramsey, L. L., and Patterson, W. I. (1946). Separation and purification of some constituents of commercial hexachlorocyclohexane. *J. Assoc. Off. Agric. Chem.* **29**, 337-346.
- Rao, P. P., Rao, M. R., Visweswariah, K., and Majumder, S. K. (1972). Comparative toxicological study of the new isolate X-factor and other components of BHC on albino rats. *Bull. Grain Technol.* **10**, 89-96.
- Rappaport, R., Schweisguth, O., Cachin, O., and Pellerin, D. (1978). Malignant supranaloma with metastases. Extraction and treatment by *o,p'*-DDD following recovery. *Arch. Fr. Pediatr.* **35**, 551-554.
- Rappolt, R. T. (1970). Use of oral DDT in three human barbiturate intoxications: CNS arousal and/or hepatic enzyme induction by reciprocal detoxicants. *Ind. Med. Surg.* **39**, 319.
- Rasmussen, J. E. (1981). The problem of lindane. *J. Am. Acad. Dermatol.* **15**, 507-516.
- Rasmussen, J. E. (1984). Pediculosis and the pediatrician. *Pediatr. Dermatol.* **2**, 74-79.
- Rasulev, I. A., Salikhov, K. K., and Barabash, Z. E. (1965). The clinical picture of hexachlorocyclohexane poisoning. *Med. Zh. Uzb.* **1**, 14-16 (in Russian).
- Ravindran, M. (1978). Toxic encephalopathy from chlorobenzilate poisoning: Report of a case. *Clin. Encephalogr.* **9**, 170-172.
- Ray, D. E., Lister, T., and Joy, R. M. (1986). The action of dieldrin on regional brain blood flow in the rat. *Pestic. Biochem. Physiol.* **25**, 205-210.
- Reach, G., Elki, F., Parry, C., Corrol, P., and Milliez, P. (1978). Increased urate excretion after *o,p'*-DDD. *Lancet* **1**, 1269.
- Read, S. T., and McKinley, W. P. (1961). DDT and DDE content of human fat. A survey. *Arch. Environ. Health* **3**, 209-211.
- Reddy, D. B., Edward, V. D., and Rao, K. V. (1966). Fatal endrin poisoning. A detailed autopsy, histopathological and experimental study. *J. Indian Med. Assoc.* **46**, 121-124.
- Reif, V. D., and Sinsheimer, J. E. (1975). Metabolism of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloro-ethane (*o,p'*-DDD) in rats. *Drug Metab. Dispos.* **3**, 15-25.
- Reif, V. D., Sinsheimer, J. E., Ward, J. C., and Scheingart, D. E. (1974). Aromatic hydroxylation and alkyl oxidation in metabolism of mitotane (*o,p'*-DDD) in humans. *J. Pharm. Sci.* **63**, 1730-1736.
- Reiner, E., Krauthacker, B., Stipcevic, M., and Stefanac, Z. (1977). Blood levels of chlorinated hydrocarbon residues in the population of a continental town in Croatia (Yugoslavia). *Pestic. Monit. J.* **11**, 54-55.
- Reiter, L. W., and Kidd, K. (1978). The behavioral effects of subacute exposure to Kepone or mirex on the weanling rat. *Toxicol. Appl. Pharmacol.* **45**, 357.
- Reiter, L. W., Kidd, K., Ledbetter, G., Chernoff, N., and Gray, L. E. (1977). Comparative behavioral toxicology of mirex and Kepone in the rat. *Toxicol. Appl. Pharmacol.* **41**, 143.
- Reiter, L. W., Kidd, K., Ledbetter, G., Gray, L. E., and Chernoff, N. (1982). Comparative behavioral toxicology of mirex and Kepone in the rat. *Toxicol. Appl. Pharmacol.* **41**, 143.
- Reuber, M. D. (1976). Histopathology of carcinomas of the liver in mice ingesting dieldrin or aldrin. *Tumori* **62**, 463-472.
- Reuber, M. D. (1977a). Histopathology of carcinomas of the liver in mice ingesting heptachlor or heptachlor epoxide. *Exp. Cell Biol.* **45**, 147-157.
- Reuber, M. D. (1977b). Hepatic vein thrombosis in mice ingesting chlorinated hydrocarbons. *Arch. Toxicol.* **38**, 163-168.
- Reuber, M. D. (1978a). Carcinogenicity of Kepone. *J. Toxicol. Environ. Health* **4**, 895-911.
- Reuber, M. D. (1978b). Carcinomas of the liver in Osborne-Mendel rats ingesting DDT. *Tumori* **64**, 571-577.
- Reuber, M. D. (1979a). Interstitial cell carcinomas of the testis in Balb/c male mice ingesting methoxychlor. *J. Cancer Res. Clin. Oncol.* **93**, 173-179.
- Reuber, M. D. (1979b). Carcinomas of the liver in Osborne-Mendel rats ingesting methoxychlor. *Life Sci.* **24**, 1367-1371.
- Reuber, M. D. (1979c). Carcinogenicity of toxaphene: A review. *J. Toxicol. Environ. Health* **5**, 729-748.
- Reuber, M. D. (1979d). Carcinomas of the liver in rat ingesting Kepone. *Neoplasia* **26**, 231-235.
- Reuber, M. D. (1980a). Carcinogenicity and toxicity of methoxychlor. *Environ. Health Perspect.* **36**, 205-219.
- Reuber, M. D. (1980b). Carcinogenicity of chlorobenzilate in mice, rats and dogs. *Clin. Toxicol.* **16**, 67-98.
- Reuber, M. D. (1980c). Significance of acute and chronic renal disease in Osborne-Mendel rats ingesting dieldrin or aldrin. *Clin. Toxicol.* **17**, 159-170.
- Reuber, M. D. (1987). Carcinogenicity of heptachlor and heptachlor epoxide. *J. Environ. Pathol. Toxicol. Oncol.* **7**, 85-114.
- Reymann, A., Brown, W., and Drager, J. (1983). Effects of DDT and dieldrin on intestinal glucose transport and brush border hydrolases. A comparison with phenobarbital and methylcholanthrene. *Biochem. Pharmacol.* **32**, 1759-1763.
- Reynolds, P. J., Lindahl, I. L., Cecil, H. C., and Bitman, J. (1975). DDT and methoxychlor accumulation and depletion in sheep. *J. Anim. Sci.* **41**, 274.
- Reynolds, P. J., Lindahl, I. L., Cecil, H. C., and Bitman, J. (1976). A comparison of DDT and methoxychlor accumulation and depletion in sheep. *Bull. Environ. Contam. Toxicol.* **16**, 240-247.
- Reznikov, A. G. (1973). Experimental data on adrenocortical activity of *m,p'*-DDD and *p,p'*-Perthane. *Probl. Endokrinol.* **19**, 71-74 (in Russian).
- Ribbens, P. H. (1985). Mortality studies of industrial workers exposed to aldrin, dieldrin and endrin. *Int. Arch. Occup. Environ. Health* **56**, 75-79.
- Richardson, A., and Robinson, J. (1971). The identification of a major metabolite of HEOD (dieldrin) in human feces. *Xenobiotica* **1**, 213-219.
- Richardson, A., Robinson, J., and Baldwin, M. K. (1970). Metabolism of endrin in the rat. *Chem. Ind. (London)*, pp. 502-503.
- Richardson, J. A., Keil, J. E., and Sandifer, S. H. (1975). Catecholamine metabolism in humans exposed to pesticides. *Environ. Res.* **9**, 290-294.
- Richter, E., Lay, J. P., Klein, W., and Korte, F. (1979). Enhanced elimination of Kepone-<sup>14</sup>C in rats fed liquid paraffin. *J. Agric. Food Chem.* **27**, 187-189.
- Richter, E., Luger, W., Klein, W., Korte, F., and Weger, N. (1981). Excretion of  $\beta$ -hexachlorocyclohexane by the rat as influenced by oral paraffin, squalene and Lutrol E 400. *Ecotoxicol. Environ. Saf.* **5**, 270-280.
- Riemschneider, R. (1952). Contact insecticides based on halogenated hydrocarbons. III. Further development of insecticides of the chlorinated-hydrocarbon class. *Euclides* **12**, 35-41, 91-105.
- Ritchey, W. R., Savary, G., and McCully, J. A. (1972). Organochlorine insecticide residues in human milk, evaporated milk, and some milk substitutes in Canada. *Can. J. Public Health* **63**, 125-132.
- Ritchey, W. R., Savary, G., and McCully, K. A. (1973). Organochlorine insecticide residues in human adipose tissue of Canadians. *Can. J. Public Health* **64**, 380-383.
- Ritchie, G. P., and Ho, I. K. (1982). Effects of chlordecone and mirex on amino acids incorporation into brain and liver proteins in the mouse. *Neurotoxicology* **3** (4), 243-248.
- Ritger, D. L. (1979). Comparison of carcinogenicity studies with aldrin and dieldrin. *J. Assoc. Off. Anal. Chem.* **62**, 900-903.
- Roan, C., Morgan, D., and Paschal, E. H. (1971). Urinary excretion of DDA following ingestion of DDT and DDT metabolites in man. *Arch. Environ. Health* **22**, 309-315.
- Robinson, J., and Hunter, C. G. (1966). Organochlorine insecticides: Concentrations in human blood and adipose tissue. *Arch. Environ. Health* **13**, 558-563.
- Robinson, J., and Roberts, M. (1969). Estimation of the exposure of the general population to dieldrin (HEOD). *Food Cosmet. Toxicol.* **7**, 501-514.
- Robinson, J., Richardson, A., Hunter, C. G., Crabtree, A. N., and Rees, H. J. (1965). Organochlorine insecticide content of human adipose tissue in southeastern England. *Br. J. Ind. Med.* **22**, 220-229.
- Robinson, J., Roberts, M., Baldwin, M., and Walker, A. I. T. (1969). The pharmacokinetics of HEOD (dieldrin) in the rat. *Food Cosmet. Toxicol.* **7**, 317-332.
- Robinson, J. R., Felton, J. S., Levitt, R. C., Thorgeirsson, S. S., and Nebert, D. W. (1975). Relationship between "aromatic hydrocarbon responsiveness" and the survival times in mice treated with various drugs and environmental compounds. *Mol. Pharmacol.* **11**, 850-865.
- Robinson, K. M., and Yarbrough, J. D. (1978a). Liver response to oral administration of mirex in rats. *Pestic. Biochem. Physiol.* **8**, 65-72.
- Robinson, K. M., and Yarbrough, J. D. (1978b). A study of mirex induced changes in liver metabolism and function with emphasis on liver enlargement. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **37**, 699.
- Robinson, K. M., and Yarbrough, J. D. (1980). Liver protein synthesis and catabolism in mirex-pretreated rats with enlarging livers. *J. Pharmacol. Exp. Ther.* **215**, 82-85.
- Robison, A. K., Mukku, V. R., Spalding, D. M., and Stancel, G. M. (1984). The estrogenic activity of DDT: The *in vitro* induction of an estrogenic-inducible protein by *o,p'*-DDT. *Toxicol. Appl. Pharmacol.* **76**, 537-543.
- Robison, A. K., Sirbasku, D. A., and Stancel, G. M. (1985a). DDT supports the growth of an estrogen-responsive tumor. *Toxicol. Lett.* **27**, 109-113.
- Robison, A. K., Schmidt, W. A., and Stancel, G. M. (1985b). Estrogenic activity of DDT: Estrogen-receptor profiles and the responses of individual uterine cell types following *o,p'*-DDT administration. *J. Toxicol. Environ. Health* **16**, 493-508.
- Roed-Petersen, J. (1974). The course of scabies during system and local steroid therapy. *Ugeskr. Laeg.* **136**, 262-263 (in Danish).
- Rogers, J. M. (1983). The effects of mirex on the neonatal rat lens *in vitro*, with a comparison to Kepone. *Toxicol. Lett.* **18**, 241-244.
- Rogers, J. M., and Grabowski, C. T. (1983). Mirex-induced fetal cataracts: Lens growth, histology and cation balance, and relationship to edema. *Teratology* **27**, 343-349.
- Rogers, J. M., and Grabowski, C. T. (1984). Postnatal mirex cataractogenesis in rats: Lens cation balance, growth and histology. *Exp. Eye Res.* **39**, 563-573.
- Rogers, J. M., Morelli, L., and Grabowski, C. T. (1984). Plasma glucose and protein concentrations in rat fetuses and neonates exposed to cataractogenic doses of mirex. *Environ. Res.* **34**, 155-161.
- Rogist, A., Vandexande, A., Gordts, L., and Beernaert, H. (1983). Organochlorine pesticide residues and PCB in maternal milk. *Arch. Belg. Med. Soc., Hyg., Med. Trav. Med. Leg.* **41**, 424-432.
- Rojanapo, W., Tepsuwan, A., Kupradinum, P., and Chutimataewin, S. (1987). Modulation of hepatocarcinogenicity of aflatoxin B<sub>1</sub> by the chlorinated insecticide, DDT. In 'Eicosanoids, Lipid Peroxidation and Cancer.' (S. K. Nigam, D. C. H. McBrien and T. F. Slater, eds.) pp. 327-338, Springer-Verlag, Berlin.
- Roncevic, N., Parkov, S., Galetin-Smith, R., Vukavic, T., Vojinovic, M., and



- Djordjevic, M. (1987). Serum concentrations of organochlorine compounds during pregnancy and the newborn. *Bull. Environ. Contam. Toxicol.* **38**, 117-124.
- Rosen, J. D., and Sutherland, D. J. (1967). The nature and toxicity of the photoconversion products of aldrin. *Bull. Environ. Contam. Toxicol.* **2**, 1-9.
- Rosenbaum, D. P., and Charles, A. K. (1986). In vitro binding of mirex by mouse hepatocytes. *J. Toxicol. Environ. Health* **17**, 385-393.
- Rosencrans, J. A., Hong, J. S., Squibb, R. E., Johnson, J. H., Wilson, W. E., and Tilton, H. A. (1982). Effects of perinatal exposure to chlordane and Kepone on neuroendocrine and neurochemical responsiveness of rats to environmental challenges. *Neurotoxicology* **3** (2), 131-142.
- Rosenstein, L., Brica, A., Rogers, N., and Lawrence, S. (1977). Neurotoxicity of Kepone in perinatal rats following in utero exposure. *Toxicol. Appl. Pharmacol.* **41**, 142-143.
- Rosival, L., Cerey, K., Rutkayova, J., Vargova, M., and Tildyova, K. (1972). Recent achievements in pesticide toxicology studies. *Egeszsegudomány* **16**, 63-69 (in Hungarian).
- Rosival, L., Barlogova, S., and Grunt, Yu. (1974). Effect of lindane on certain immunological reactions in rats. *Gig. Tr. Prof. Zabol.* **6**, 53-55 (in Russian).
- Ross, C. M. (1964). Sock dermatitis from dieldrin. *Br. J. Dermatol.* **76**, 494-495.
- Rossi, L., Ravera, M., Repetti, G., and Santi, L. (1977). Long-term administration of DDT or phenobarbital-Na in Wistar rats. *Int. J. Cancer* **19**, 179-185.
- Rossi, L., Barbieri, O., Sanguineti, M., Cabral, J. R. P., Bruzzi, P., and Santi, L. (1983). Carcinogenicity study with technical-grade dichlorophenyltrichloroethane and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene in hamsters. *Cancer Res.* **43**, 776-781.
- Rothe, C. F., Mattson, A. M., Nueslein, R. M., and Hayes, W. J., Jr. (1957). Metabolism of chlorophenothane (DDT): Intestinal lymphatic absorption. *Arch. Ind. Health* **16**, 82-86.
- Roux, F., Treich, I., and Fournier, F. (1980). Different levels of changes induced by the insecticide lindane in cultured C-6 glioma cells. *Toxicology* **17**, 261-264.
- Rowley, D. L., Rab, M. A., Hardjotanojo, W., Liddle, J., Bur, V. W., Saleem, M., Sokal, D., Falk, H., and Head, S. L. (1987). Convulsions caused by endrin poisoning in Pakistan. *Pediatrics* **79**, 928-934.
- Rozin, D. G., and Satyvaldiyev, A. S. (1970). A case of acute poisoning with BHC. *Med. Zh. Uzb.* **7**, 74 (in Russian).
- Rozman, K. K. (1984). Phase II enzyme induction reduces body burden of heptachlor in rats. *Toxicol. Lett.* **20**, 5-12.
- Rumsey, T. S., and Bond, J. (1972). Effect of aldrin, urea and DES on the physiology of beef heifers fed a concentrate or roughage diet. *J. Anim. Sci.* **35**, 978-985.
- Rumsey, T. S., and Schreiber, E. C. (1969). Excretion of radiocarbon of C-14-labeled 16- $\alpha$ -dihydroxyprogesterone acetophenide (DHPA) by beef heifers. *J. Agric. Food Chem.* **17**, 1210-1212.
- Runhaar, E. A., Sangster, B., Greve, P. A., and Voortman, M. (1985). A case of fetal endrin poisoning. *Hum. Toxicol.* **4**, 241-247.
- Rybakova, M. N. (1968). The effect of certain pesticides on the hypophysis and its gonadotrophic function. *Gig. Sanit.* **33**, 27-31 (in Russian).
- Sadriyeva, R. V., Absalyamov, I. F., and Flebkashanskaya, N. V. (1971). The dynamics of morphological changes in the nasal mucous membrane in prolonged peroral administration of small doses of hexachlorane. *Vestn. Otorinolaringo.* **33**, 92-95 (in Russian).
- Saez, J. M., Loras, B., Morera, A. M., and Bertrand, J. (1971). Studies of androgens and their precursors in adrenocortical virilizing carcinoma. *J. Clin. Endocrinol. Metab.* **32**, 462-469.
- Sagelsdorff, P., Lutz, W. K., and Schlatter, C. (1983). The relevance of covalent binding to mouse liver DNA to the carcinogenic action of hexachlorocyclohexane isomers. *Carcinogenesis (London)* **4**, 1267-1273.
- Saigal, S., Bhatnagar, V. K., and Singh, V. S. (1985). Effects of lindane and Diazinon on transaminases in rats. *Environ. Ecol.* **3**, 408-410.
- Saito, I., Kawamura, N., Uno, K., Hisanaga, N., Takeuchi, Y., Ono, Y., Iwata, M., Gotoh, M., Okutani, H., Matsumoto, T., Fukaya, Y., Yoshitomi, S., and Ohno, Y. (1986). Relationship between chlordane and its metabolites in blood of pest control operators and spraymen. *Int. Arch. Occup. Environ. Health* **58**, 91-97.
- Saitoh, K., Shaw, S., and Tilton, H. A. (1986). Noradrenergic influence on the prepulse inhibition of acoustic startle. *Toxicol. Lett.* **34**, 209-216.
- Saleh, M. A. (1980). Isomerization of lindane by reduced hematin. *Bull. Environ. Contam. Toxicol.* **25**, 833-836.
- Saleh, M. A., and Casida, J. E. (1977a). Consistency of toxaphene composition analysed by open tubular column gas-liquid chromatography. *J. Agric. Food Chem.* **25**, 63-68.
- Saleh, M. A., Turner, W. V., and Casida, J. E. (1977). Polychlorobornane components of toxaphene: Structure toxicity relations and metabolic reductive dechlorination. *Science* **198**, 1256-1258.
- Saleh, M. A., Skinner, R. F., and Casida, J. E. (1979). Comparative metabolism of 2,2,5-endo,6-exo,8,9,10-heptachlorobornane and toxaphene in six mammalian species and chickens. *J. Agric. Food Chem.* **27**, 731-737.
- Salikhodzhaev, S. S., and Fershtat, V. N. (1972). Condition of the olfactory analyzer under the effect of organochlorine and organophosphorus pesticides. *Gig. Sanit.* **37**, 95-96 (in Russian).
- Samosh, L. V. (1974). Chromosome aberrations and the character of satellite associations following accidental exposure of the human body to polychlorocamphene. *Tsitol. Genet.* **8**, 24-27 (in Russian).
- Samosh, L. V. (1981). Chromosomal aberrations in the lymphocytes of workers during the use of polychloroprene in agriculture. *Tsitol. Genet.* **15**, 62-67 (in Russian).
- Sampson, D. A., Pitas, R. E., and Jensen, R. G. (1980). Effect of chronic ingestion of DDT on physiological and biochemical aspects of fatty acid deficiency. *Lipids* **15**, 815-822.
- Samuels, A. J., and Milby, T. H. (1971). Human exposure to lindane: Clinical, hematological and biochemical effects. *J. Occup. Med.* **13**, 147-151.
- Sanborn, G. E., Selhorst, J. B., Calabrese, V. P., and Taylor, J. R. (1979). Pseudotumor cerebri and insecticide intoxication. *Neurology* **29**, 1222-1227.
- Sánchez-Medal, L., Castaneda, J. P., and García-Rojas, F. (1963). Insecticides and aplastic anemia. *N. Engl. J. Med.* **269**, 1365-1367.
- Sandifer, S. H. (1974). Industrial and agricultural chemicals. *Pediatrics* **53**, 843-844.
- Sandifer, S. H., Cupp, C. M., Wilkins, R. T., Loadholt, B., and Schuman, S. H. (1981). A case-control study of persons with elevated blood levels of dieldrin. *Arch. Environ. Contam. Toxicol.* **10**, 35-45.
- Santolucito, J. A., and Morrison, G. (1971). EEG of rhesus monkeys following prolonged low-level feeding of pesticides. *Toxicol. Appl. Pharmacol.* **19**, 147-154.
- Sanyal, S., Agarwal, N. J., and Subrahmanyam, D. (1986). Effect of acute sublethal and chronic administration of DDT (chlorophenothane) on brain lipid metabolism of rhesus monkeys. *Toxicol. Lett.* **34**, 47-54.
- Sarett, H. P., and Jandorf, B. J. (1947). Effect of chronic DDT intoxication in rats on lipids and other constituents of the liver. *J. Pharmacol. Exp. Ther.* **91**, 340-344.
- Sarkander, H. I. (1974). Temporal relationship between rat liver histone acetylation and nuclear RNA polymerase activities after  $\alpha$ -hexachlorocyclohexane application. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **282**, R83.
- Sarkander, H. I., Kemmerle, M., and Brade, W. (1974). Rat liver histone modifications and their relationship to DNA-dependent RNA polymerase activities during  $\alpha$ -hexachlorocyclohexane induced liver proliferation. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **284**, 39-53.
- Sato, H., Toyoda, K., Furukawa, F., Hasegawa, R., Takahashi, M., and Hayashi, Y. (1987). Subchronic oral toxicity test of dicofol (1,1-bis(p-chlorophenyl)-2,2,2-trichloroethanol) as the basis for the design of a long-term carcinogenicity study in B6C3F1 mice. *Eisei Shikensho Hokoku* (105), 42-45 (in Japanese).
- Sauter, E. A., and Steele, E. E. (1972). The effect of low level pesticide feeding on the fertility and hatchability of chicken eggs. *Poult. Sci.* **51**, 71-76.
- Savage, E. P., Bagby, J. R., Jr., Mounce, L., Williams, L. P., Jr., Cholas, P. H., and Cholas, G. (1971). Pesticide poisonings in rural Colorado. *Rocky Mt. Med. J.* **68**, 29-33.
- Savage, E. P., Tessari, J. D., Malberg, J. W., Wheeler, H. W., and Bagby, J. R. (1973). Organochlorine pesticide residues and polychlorinated biphenyls in human milk. *Pestic. Monit. J.* **7**, 1-5.
- Savage, E. P., Keefe, T. J., Tessari, J. D., Wheeler, H. W., Applehans, F. M., Goes, E. A., and Ford, S. A. (1981). National study of chlorinated hydrocarbon insecticide residues in human milk, U.S.A. I. Geographic distribution of dieldrin, heptachlor, heptachlor epoxide, chlordane, oxychlordane, and mirex. *Am. J. Epidemiol.* **113**, 413-422.
- Saxena, M. C., Siddiqui, M. K. J., Agarwal, V., and Kuuty, D. (1983). A comparison of organochlorine insecticide contents in specimens of maternal blood, placenta and umbilical-cord blood from stillborn and liveborn cases. *J. Toxicol. Environ. Health* **11**, 71-79.
- Saxena, S. P., Khare, C., Farooq, A., Murugesan, K., Buckshee, K., and Chandra, J. (1987a). DDT and its metabolites in leiomyomatous and normal human uterine tissue. *Arch. Toxicol.* **59**, 453-455.
- Saxena, S. P., Share, C., Farooq, A., Murugesan, K., and Chandra, J. (1987b). DDT residues in blood of residents of areas surrounding a DDT manufacturing factory in Delhi. *Bull. Environ. Contam. Toxicol.* **38**, 392-395.
- Schäfer, M. L., and Campbell, J. E. (1966). Distribution of pesticide residues in human body tissues from Montgomery County, Ohio. *Adv. Chem. Ser.* **60**, 89-98.
- Schechter, R. D., Stabenfeldt, G. H., Gribble, D. H., and Ling, G. V. (1973). Treatment of Cushing's syndrome in the dog with adrenocorticolytic agent (*o,p'*-DDD). *J. Am. Vet. Med. Assoc.* **162**, 629-639.
- Scheufler, E., and Rozman, K. (1984). Enhanced total body clearance of heptachlor from rats by stilbeneoxide. *Toxicology* **32**, 93-104.
- Scheuing, G., and Vogelbach, G. (1950).  $\gamma$ - and  $\delta$ -Hexachlorocyclohexane. Odor components of technical hexachlorocyclohexanes. *Naturwissenschaften* **37**, 211-212 (in German).
- Schick, M. (1973). Survival with adrenal carcinoma. *JAMA, J. Am. Med. Assoc.* **224**, 1763.
- Schimmel, M., Abrahamov, A., and Brama, I. (1980). A rare complication of aplastic anemia due to lindane intoxication. *Harefuah* **98**, 355-356 (in Hebrew).
- Schmidt, R. (1973). Effect of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) on the prenatal development of the mouse (under consideration of distribution of tritium-labeled and carbon-14-labeled DDT in pregnant mice). *Biol. Rundsch.* **11**, 316-317 (in German).
- Schnorr, J. K. (1973). Effects of dieldrin on learning and retention of a visual discrimination task in sheep. *Diss. Abstr. Int. B* **33**, 3995B.
- Schoor, W. P. (1970). Effect of anticonvulsant drugs on insecticide residues. *Lancet* **2**, 520-521.
- Schroeder, G., and Dorozalska, A. (1975). Degradation of DDT and its analogues. *Wiad. Chem.* **29**, 553-565.
- Schröter, C., Parzefall, W., Schröter, H., and Schulte-Hermann, R. (1987). Dose-response studies on the effects of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -hexachlorocyclohexane on putative preneoplastic foci monooxygenases, and growth in rat livers. *Cancer Res.* **47**, 80-88.
- Schulte-Hermann, R. (1974). Control by feeding habits of the induction of hepatic DNA synthesis by  $\alpha$ -hexachlorocyclohexane. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **282**, R88.
- Schulte-Hermann, R. (1985). Tumor promotion in liver. *Arch. Toxicol.* **57**, 147-158.
- Schulte-Hermann, R., and Parzefall, W. (1981). Failure to discriminate initiation from promotion of liver tumours in a long-term study with the phenobarbital-type inducer  $\alpha$ -hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. *Cancer Res.* **41**, 4140-4146.
- Schulte-Hermann, R., Koransky, W., Leberl, C., and Noack, G. (1971). Hyperplasia and hypertrophy of rat liver induced by  $\alpha$ -hexachlorocyclohexane and butylhydroxytoluene. Retention of the hyperplasia during involution of the enlarged organ. *Virchows Arch. B* **9**, 125-134.
- Schulte-Hermann, R., Schlicht, I., Koransky, W., Leberl, C., Eulenstedt, C., and Zimek, M. (1972). Selective inhibition of liver-cell proliferation by CFT 1201 and SKF 525 A. Studies on growth processes induced by drugs and by partial hepatectomy. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **273**, 109-122.
- Schulte-Hermann, R., Leberl, C., Langgraf, H., and Koransky, W. (1974). Liver growth and mixed-function oxidase activity: Dose-dependent stimulatory and inhibitory effects of  $\alpha$ -hexachlorocyclohexane. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **285**, 355-366.
- Schupan, I., Ballschmiter, K., and Tolo, G. (1968). Some metabolites of endosulfans in rats and mice. *Z. Naturforsch., C: Biochem., Biophys., Biol., Virol.* **23c**, 701-707 (in German).
- Schüttmann, W. (1968). Chronic liver damage after occupational exposure to dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH). *Int. Arch. Gewerbepathol. Gewerbehyg.* **24**, 193-210 (in German).
- Schwabe, U., and Wendling, I. (1967). Increased metabolism of drugs by small doses of DDT and other chlorinated hydrocarbon insecticides. *Arzneim.-Forsch.* **17**, 614-618 (in German).
- Schwär, T. G. (1965). Intravenous dieldrin solution administration. *J. Forensic Med.* **12**, 142-145.
- Scott, J. L., Cartwright, G. E., and Wintrobe, N. M. (1959). Acquired aplastic anemia: An analysis of thirty-nine cases and a review of the pertinent literature. *Medicine (Baltimore)* **38**, 119-172.
- Scotti, T. M., Chernoff, N., Linder, R., and McElroy, W. K. (1981). Histopathologic lens changes in mirex-exposed rats. *Toxicol. Lett.* **9**, 289-294.
- Sedlak, V. A. (1965). Solubility of benzene hexachloride isomers in rat fat. *Toxicol. Appl. Pharmacol.* **7**, 79-83.
- Seiber, J. N., Landrum, P. F., Madden, S. C., Nugent, K. D., and Winterlin, W. L. (1975). Isolation and gas chromatographic characterization of some toxaphene components. *J. Chromatogr.* **114**, 361-368.
- Selby, L. A., Newell, K. W., Hauser, G. A., and Junker, G. (1969). Comparison of chlorinated hydrocarbon pesticides in maternal blood and placental tissues. *Environ. Res.* **2**, 247-255.
- Sell, J. L., Davison, K. L., and Puyear, R. L. (1971). Aniline hydroxylase, N-demethylase and cytochrome P<sub>450</sub> in liver microsomes of hens fed DDT and dieldrin. *J. Agric. Food Chem.* **19**, 58-60.
- Serat, W. F., Lee, M. K., Van Loon, A. J., Mengle, D. C., Ferguson, J., Burks, J. M., and Bender, T. R. (1977). DDT and DDE in the blood and diet of Eskimo children from Hooper Bay, Alaska. *Pestic. Monit. J.* **11**, 1-4.
- Serrone, D. M., Stein, A. A., and Coulston, F. (1965). Biochemical and electron microscopic changes observed in rats and monkeys medicated orally with methoxychlor. *Toxicol. Appl. Pharmacol.* **7**, 497.
- Seth, P. K., Saidi, N. F., Agrawal, A. K., and Anand, M. (1986). Neurotoxicity of endosulfan in young and adult rats. *Neurotoxicology* **7** (2), 623-635.
- Shabad, L. M., Kolesnichenko, T. S., and Nikonova, T. V. (1972). On a possible blastomogenicity of DDT. *Vopr. Pitan.* **30**, 63-66 (in Russian).
- Shacter, B. (1981). Treatment of scabies and pediculosis with lindane preparations: An evaluation. *J. Am. Acad. Dermatol.* **5**, 517-527.
- Shah, P. V., Monroe, R. J., and Guthrie, F. E. (1981). Comparative rates of dermal penetration of insecticides in mice. *Toxicol. Appl. Pharmacol.* **59**, 414-423.
- Shankland, D. L. (1982). Neurotoxic action of chlorinated hydrocarbon insecticides. *Neurobehav. Toxicol. Teratol.* **4**, 805-811.
- Sharma, R. P. (1976). Influence of dieldrin on serotonin turnover and 5-hydroxyindole acid efflux in mouse brain. *Life Sci.* **19**, 537-542.
- Sheehan, H. L., Summers, V. K., and Nichols, J. (1953). DDD therapy in Cushing's syndrome. *Lancet* **1**, 312-314.
- Shemesh, Y., Bourvine, A., Gold, D., and Bracha, P. (1989). Survival after acute endosulfan intoxication. *J. Toxicol. Clin. Toxicol.* **26**, 265-268.
- Shilina, V. F. (1973). Effect of lindane on the serotonin level in the blood and tissues of rats. *Farmakol. Toksikol. (Moscow)* **36**, 687-688 (in Russian).
- Shimamoto, T., Matsueda, H., Yoshinouchi, M., Okinaga, E., Mori, K., Yamatake, S., Nakajima, S., and Aihara, M. (1973). Results of a survey on PCB and organochlorine pesticide residues in mothers' milk. *Annu. Rep. Ehime Prefect. Inst. Hyg. Sci.* **35**, 71-73 (in Japanese).
- Shimizu, S. (1972).  $\beta$ -BHC residues in human milk and an attempt to reduce the residue by serving diets low in  $\beta$ -BHC content. *Jpn. J. Public Health* **19**, 376-382 (in Japanese).
- Shimizu, S. (1974). Results of pursuing investigation on pesticide residues in Saga Prefecture. *Jpn. J. Public Health* **21**, 239-245.
- Shindell, S., and Ulrich, S. (1986). Mortality of workers employed in the manufacture of chlordane: An update. *J. Occup. Med.* **28**, 497-501.



- Shindell, S., Ulrich, I. S., and Geifer, E. E. (1981). Epidemiology of chlorinated hydrocarbon insecticides. In "Toxicology of Halogenated Hydrocarbons: Health and Ecological Effects" (M. A. Q. Kahn and R. H. Stanton, eds.), Pergamon, New York.
- Shindo, H. (1972). Applications of whole body autoradiography to the studies of drug metabolism and disposition. *Annu. Rep. Sankyo Res. Lab.* **24**, 1-72 (in Japanese).
- Shiota, K., Tanimura, T., Nishimura, H., Mizutani, T., and Matsumoto, M. (1974). Polychlorinated biphenyls, BHC, and DDE in human fetal tissues. *Congenital Anom.* **13**, 179.
- Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A., and Kada, T. (1976). Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.* **40**, 19-30.
- Shirasu, Y., Moriya, M., Kato, K., Lienard, F., Tezuka, H., Teramoto, S., and Kada, T. (1977). Mutagenicity screening of pesticides and modification products: A basis of carcinogenicity evaluation. *Cold Spring Harbor Conf. Cell Proliferation* **4**.
- Shivanandappa, T., and Krishnakumari, M. K. (1983). Hexachlorocyclohexane-induced testicular dysfunction in rats. *Acta Pharmacol. Toxicol.* **52**, 12-17.
- Shivanandappa, T., Krishnakumari, M. K., and Majumder, S. K. (1982). Inhibition of steroidogenic activity in the adrenal cortex of rats fed benzene hexachloride (hexachlorocyclohexane). *Experientia* **38**, 1251-1253.
- Shul'ga, A. I. (1957). On the problem of BHC poisoning. *Klin. Med. (Moscow)* **5**, 139-142 (in Russian).
- Shure, K. A., and Law, A. (1977). DDT residues in adipose tissue of people in Rangoon area. *Southeast Asian J. Trop. Med. Public Health* **8**, 71-73.
- Siddiqui, M. K. J., Saxena, M. C., Bhargava, A. K., Seth, T. D., Krishna Murti, C. R., and Kutty, D. (1981). Agrochemicals in the maternal blood, milk and cord blood: A source of toxicants for prenatals and neonates. *Environ. Res.* **24**, 24-32.
- Sieber, S. M. (1976). The lymphatic absorption of *p,p'*-DDT and some structurally-related compounds in the rat. *Pharmacology* **14**, 443-454.
- Sieber, S. M., Cohn, V. H., and Wynn, W. T. (1974). The entry of foreign compounds into the thoracic duct lymph of rat. *Xenobiotica* **4**, 265-284.
- Siegers, C. P., Schumann, S., Thies, E., Böse-Younes, H., and Younes, M. (1984). Aldrin epoxidase and dimethylhydrazine demethylase activities in tumorous and non-tumorous tissue of the human colon and rectum. *Cancer Lett.* **23**, 39-43.
- Sierra, V., and Uphouse, L. (1986). Long-term consequences of neonatal exposure to chlordane. *Neurotoxicology* **7** (2), 609-622.
- Simmons, J. H., and Tatton, J. O. (1966). Organochlorine pesticides in gallstones. *Clin. Chem. (Winston-Salem, N.C.)* **12**, 697-700.
- Simmons, S. W. (1959). The use of DDT insecticides in human medicine. In "DDT: The Insecticide Dichlorodiphenyl-trichloroethane and Its Significance" (P. Müller, ed.), Vol. 2, pp. 251-502. Birkhaeuser, Basel.
- Simon, G. S., Kipps, B. R., Tarcliff, R. G., and Borzelleca, J. F. (1978). Failure of Kepone and hexachlorobenzene to induce dominant lethal mutations in the rat. *Toxicol. Appl. Pharmacol.* **45**, 330-331.
- Simon, G. S., Egle, J. L., Dougherty, R. W., and Borzelleca, J. F. (1986). Dominant lethal assay of chlordane and its distribution in the male reproductive tissues of the rat. *Toxicol. Lett.* **30**, 237-245.
- Simpson, G. R., and Shandar, A. (1972). Exposure to chlorinated hydrocarbon pesticides by pest control operators. *Med. J. Aust.* **2**, 1060-1063.
- Sinclair, P. R., and Granick, S. (1974). Uroporphyrin formulation induced by chlorinated hydrocarbons (lindane, polychlorinated biphenyls, tetrachlorodibenzo-*p*-dioxin). Requirements for endogenous iron, protein synthesis and drug-metabolizing activity. *Biochem. Biophys. Res. Commun.* **61**, 124-133.
- Singh, A., Villeneuve, D. C., Bhatnagar, M. K., and Valli, V. E. O. (1982). Ultrastructure of the thyroid glands of rats fed photomirex: An 18 month recovery study. *Toxicology* **23**, 309-319.
- Singh, A., Bhatnagar, M. K., Villeneuve, D. C., and Valli, V. E. (1985). Ultrastructure of the thyroid glands of rats fed photomirex: A 48-week recovery study. *J. Environ. Pathol. Toxicol. Oncol.* **6**, 115-126.
- Singh, K. K., Jha, G. J., Chauhan, H. V. S., and Singh, P. N. (1985). Pathology of chronic aldrin intoxication in goats. *Zentralbl. Veterinärmed.* **32**, 437-444.
- Singhal, R. L., and Kacew, S. (1976). The role of cyclic AMP in chlorinated hydrocarbon-induced toxicity. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **35**, 2618-2623.
- Sinsheimer, J. E., Guilford, J., Bobrin, L. D., and Scheingart, D. E. (1972). Identification of *o,p'*-dichloro-diphenylacetic acid as a urinary metabolite of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane. *J. Pharm. Sci.* **61**, 314-316.
- Sirica, A. E., Wilkerson, C. S., Wu, L. L., Fitzgerald, R., Blanke, R. V., and Guzelian, P. S. (1989). Evaluation of chlordane in a two-stage model of hepatocarcinogenesis: A significant sex difference in the hepatocellular carcinoma incidence. *Carcinogenesis (London)* **10**, 1047-1054.
- Siyali, D. S. (1972). Hexachlorobenzene and other organochlorine pesticides in human blood. *Med. J. Aust.* **2**, 1063-1066.
- Siyali, D. S., and Simon, R. E. (1973). Chlorinated hydrocarbon pesticides in human blood and fat. *Med. J. Aust.* **1**, 212-213.
- Siyali, D. S., Stricker, P., and Tischler, E. (1974). Placental barrier reduced pesticide intake to fetus. *Med. J. Aust.* **1**, 285.
- Sizonenko, P. C., Doret, A. M., Riondel, A. M., and Paunier, L. (1974). Cushing's syndrome due to bilateral adrenal cortical hyperplasia in a 13-year-old girl: Successful treatment with *o,p'*-DDD. *Helv. Paediatr. Acta* **29**, 195-202.
- Skaare, J. U. (1981). Persistent organochlorinated compounds in Norwegian human milk in 1979. *Acta Pharmacol. Toxicol.* **49**, 384-389.
- Skaare, J. U., Tuveng, J. M., and Sande, H. A. (1988). Organochlorine pesticides and polychlorinated biphenyls in maternal adipose tissue, blood, milk and cord blood from mothers and their infants living in Norway. *Arch. Environ. Contam. Toxicol.* **17**, 55-63.
- Skalsky, H. L., Fariss, M. W., Blanke, R. V., and Guzelian, P. S. (1979). The role of plasma proteins in the transport and distribution of chlordane (Kepone) and other polyhalogenated hydrocarbons. *Ann. N.Y. Acad. Sci.* **320**, 231-237.
- Skromme-Kadlubik, G., Alvarez-Cervera, J., and Cortes-Marmolejo, F. (1972). Studies of suprarenal scintigraphy in humans using <sup>131</sup>I-DDD. *J. Nucl. Med.* **13**, 282-284.
- Skromme-Kadlubik, G., Alvarez-Cervera, J., and Cortes-Marmolejo, F. (1973a). Human suprarenal gammagrams using DDD labeled with <sup>131</sup>I. *Arch. Inst. Cardiol. Mex.* **43**, 245-248.
- Skromme-Kadlubik, G., Alvarez-Cervera, J., and Cortes-Marmolejo, F. (1973b). Adrenal scanning with dichloro-diphenyl-dichloroethane-<sup>131</sup>I(DDD-<sup>131</sup>I)—a clinical report on 100 subjects. *Int. J. Nucl. Med. Biol.* **2**, 83-96.
- Skromme-Kadlubik, G., Ferez, A., and Celis, C. (1974). Selective atrophy of adrenal cortex by dichloro-diphenyl dichloroethane I-131 (DDD-I-131). *Arch. Inst. Cardiol. Mex.* **44**, 869-873.
- Slade, R. E. (1945). The  $\gamma$ -isomer of hexachlorocyclohexane (Gammexane). An insecticide with outstanding properties. *Chem. Ind. (London)*, pp. 314-319.
- Slooten, H. V., Seters, A. P. V., Smeenk, D., and Moolenaar, A. J. (1982). *o,p'*-DDD (mitotane) levels in plasma and tissues during chemotherapy and at autopsy. *Cancer Chemother. Pharmacol.* **9**, 85-88.
- Smialowicz, R. J., Luebka, R. W., Riddle, M. M., Rogers, R. R., and Rowe, D. G. (1985). Evaluation of the immunotoxic potential of chlordane with comparison to cyclophosphamide. *J. Toxicol. Environ. Health* **15**, 561-574.
- Smith, M. I., and Stohlman, E. F. (1944). The pharmacologic action of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane and its estimation in the tissues and body fluids. *Public Health Rep.* **59**, 984-993.
- Smith, M. I., and Stohlman, E. F. (1945). Further studies on the pharmacologic action of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT). *Public Health Rep.* **60**, 289-301.
- Smith, M. I., Bauer, H., Stohlman, E. F., and Lillie, R. D. (1946). The pharmacologic action of certain analogues and derivatives of DDT. *J. Pharmacol.* **88**, 359-365.
- Smith, R. B., Larson, P. S., Finnegan, J. K., Haag, H. B., Hennigar, R. G., and Cobey, F. (1959). Toxicological studies on 2,2-bis(chlorophenyl)-2,2,2-trichloroethanol (Kelthane). *Toxicol. Appl. Pharmacol.* **1**, 119-134.
- Smith, R. J. (1982). Hawaiian milk contamination creates alarm. *Science* **217**, 137-140.
- Smith, R. M., Cunningham, W. L., Van Gelder, G. A., and Karas, G. G. (1976). Dieldrin toxicity and successive discrimination reversal in squirrel monkeys (*Saimiri sciureus*). *J. Toxicol. Environ. Health* **1**, 737-747.
- Smrek, A. L., Adams, S. R., Liddle, J. A., and Kimbrough, R. D. (1977). Pharmacokinetics of mirex in goats. 1. Effect of reproduction and lactation. *J. Agric. Food Chem.* **25**, 1321-1325.
- Smrek, A. L., Adams, S. R., Liddle, J. A., and Kimbrough, R. D. (1978). Pharmacokinetics of mirex in goats. 2. Residue tissue levels, trans-placental passage during recovery. *J. Agric. Food Chem.* **26**, 945-947.
- Sobti, R. C., Krishan, A., and Davies, J. (1983). Cytokinetic and cytogenetic effects of agricultural chemicals on human lymphoid cells *in vitro*. II. Organochlorine pesticides. *Arch. Toxicol.* **52**, 221-231.
- Soennichsen, N., Barthelme, R., and Barthelme, H. (1970). Studies on the currently increased occurrence and clinical and therapeutic aspects of scabies. *Dtsch. Gesundheitswes.* **28**, 1178-1183 (in German).
- Soine, P. J., Blanke, R. V., Guzelian, P. S., and Schwartz, C. C. (1982). Preferential binding of chlordane to the protein and high density lipoprotein fractions of plasma from humans and other species. *J. Toxicol. Environ. Health* **9**, 107-118.
- Soine, P. J., Blanke, R. V., and Schwartz, C. C. (1983). Chlordane metabolism in the pig. *Toxicol. Lett.* **17**, 35-41.
- Soos, K., Cielezsky, V., and Tarjan, R. (1972). The development of the level of chlorinated hydrocarbons in the adipose tissue of the population of Budapest in 1970. *Egeszsegstudomány* **16**, 70-76 (in Hungarian).
- Sosinerz, M., Szczurek, Z., Knapke, R., and Kolodziejczyk, A. (1972). Morphologic studies on short-term subacute toxicity of Kamfochlor. *Patol. Pol.* **23**, 199-202 (in Polish).
- Sotaniemi, E. A., Medzihradsky, F., and Eliasson, G. (1974). Glucaric acid as an indicator of use of enzyme-inducing drugs. *Clin. Pharmacol. Ther.* **15**, 417-423.
- Southern, A. L., Weisenfeld, S., Laufer, A., and Goldner, M. G. (1961). Effect of *o,p'*-DDD in a patient with Cushing's syndrome. *J. Clin. Endocrinol. Metab.* **21**, 201-208.
- Southern, A. L., Tochimoto, S., Isurugi, K., Gorch, G. G., Krikun, E., and Stypulkowski, W. (1966a). The effect of 2,2-bis-(2-chlorophenyl)-4-chlorophenyl)-1,1,1-trichloroethane (*o,p'*-DDD) on the metabolism of infused cortisol-7-H. *Steroids* **7**, 11-29.
- Southern, A. L., Tochimoto, S., Strom, L., Ratuschni, A., Rass, H., and Gorch, G. (1966b). Remission in Cushing's syndrome with *o,p'*-DDD. *J. Clin. Endocrinol. Metab.* **26**, 268-278.
- Sovocool, G. W., Lewis, R. G., Harless, R. L., Wilson, N. K., and Zehr, R. D. (1977). Analysis of technical chlordane by gas chromatography mass spectrometry. *Anal. Chem.* **49**, 734-740.
- Speck, L. B., and Maaske, C. A. (1958). The effects of chronic and acute exposure of rats to endrin. *AMA Arch. Ind. Health* **18**, 268-272.
- Spencer, W. F., and Cliath, M. M. (1970). Vapor density and apparent vapor pressure of lindane (gamma-BHC). *J. Agric. Food Chem.* **18**, 529-530.
- Sperling, F., Ewenike, H. K. U., and Farber, T. (1972). Changes in LD 50 of parathion and heptachlor following turpentine pretreatment. *Environ. Res.* **5**, 164-171.
- Spicer, S. S., Sweeney, T. R., von Oettingen, W. F., Lillie, R. D., and Neal, P. A. (1947). Toxicological observations on goats fed large doses of DDT. *Vet. Med. (Prague)* **42**, 289-293.
- Spindler, M. (1983). DDT: Health aspects in relation to man and risk/benefit assessment based thereupon. *Residue Rev.* **90**, 1-34.
- Spiotto, E. J. (1951). Aldrin poisoning in man. Report of a case. *Arch. Ind. Hyg. Occup. Med.* **4**, 560-566.
- Spyker-Cranmer, J. M., Barnett, J. B., Avery, D. L., and Cranmer, M. F. (1982). Immunotoxicology of chlordane: Cell-mediated and humoral immune responses in adult mice exposed *in utero*. *Toxicol. Appl. Pharmacol.* **62**, 402-408.
- Squibb, R. E., and Tilson, H. A. (1982a). Effects of gestational and perinatal exposure to chlordane (Kepone) on the neurobehavioral development of Fischer-344 rats. *Neurotoxicology* **3** (2), 17-26.
- Squibb, R. E., and Tilson, H. A. (1982b). Neurobehavioral changes in adult Fischer-344 rats exposed to dietary levels of chlordane (Kepone): A 90 day chronic dosing study. *Neurotoxicology* **3** (2), 59-65.
- Sram, R. (1974). Evaluation of the genetic danger of chemical substances. *Gig. Sanit.* **4**, 80-83 (in Russian).
- Srinivasan, K., and Radhakrishnamurthy, R. (1983a). Studies on the distribution of the  $\beta$ - and  $\gamma$ -isomers of hexachlorocyclohexane. *J. Environ. Sci. Health, Part B* **18**, 401-418.
- Srinivasan, K., and Radhakrishnamurthy, R. (1983b). Induction of liver mixed function oxygenase system by  $\beta$ - and  $\gamma$ -hexachlorocyclohexane. *Indian J. Biochem. Biophys.* **20**, 84-91.
- Srinivasan, K., Ramesh, H. P., and Radhakrishnamurthy, R. (1984). Renal tubular dysfunction caused by dietary hexachlorocyclohexane (HCH) isomers. *J. Environ. Sci. Health, Part B* **19**, 453-466.
- Srivastava, A. S. (1952). Metabolic relationship between *meso*-inositol and lindane. *Science* **115**, 403-404.
- Stacey, C. I., and Tatum, T. (1985). House treatment with organochlorine pesticides and their levels in human milk—Perth, Western Australia. *Bull. Environ. Contam. Toxicol.* **35**, 202-208.
- Stacey, C. I., and Thomas, B. W. (1975). Organochlorine pesticide residues in human milk, Western Australia 1970-71. *Pestic. Monit. J.* **9**, 64-66.
- Stacey, C. I., Perriman, W. S., and Whitney, S. (1985). Organochlorine pesticide residue levels in human milk: Western Australia, 1979-1980. *Arch. Environ. Health* **40**, 102-108.
- Stammers, F. M. G., and Whitfield, F. G. S. (1947). Toxicity of DDT to man and animals. *Bull. Entomol. Res.* **38**, 1-73.
- Stanton, R. H., and Khan, M. A. Q. (1972). Oxidation of cyclodiene insecticides by sunfish, mouse and rat liver mixed-function oxidase. *Am. Zool.* **12**, 38.
- Stark, L. G., Joy, R. M., and Albertson, T. E. (1983). The persistence of kindled amygdaloid seizures in rats exposed to lindane. *Neurobehav. Toxicol. Teratol.* **4**, 221-226.
- Stark, L. G., Albertson, T. E., and Joy, R. M. (1986). Effects of hexachlorocyclohexane isomers on the acquisition of kindled seizures. *Neurobehav. Toxicol. Teratol.* **8**, 487-491.
- Stark, L. G., Chuang, R. Y., and Joy, R. M. (1987a). Biochemical markers of exposure to proconvulsant and anticonvulsant chlorinated hydrocarbons. *Epilepsia* **8**, 44.
- Stark, L. G., Joy, R. M., and Hollings, M. A. (1987b). Effects of two isomers of hexachlorocyclohexane (HCH) on cortical beta-adrenoceptors in rat brain. *Exp. Neurol.* **98**, 276-284.
- Starr, H. G., Jr., and Clifford, N. J. (1971). Absorption of pesticides in a chronic skin disease. *Arch. Environ. Health* **22**, 396-400.
- Starr, H. G., Jr., and Clifford, N. J. (1972). Acute lindane intoxication. A case study. *Arch. Environ. Health* **25**, 374-375.
- Steentoft, A. (1979). A case of fatal dieldrin poisoning. *Med. Sci. Law* **19**, 268-269.
- Stehr-Green, P. A., Wohlleb, J. C., Royce, W., and Head, S. L. (1988). An evaluation of serum pesticide residue levels and liver function in persons exposed to dairy products contaminated with heptachlor. *JAMA, J. Am. Med. Assoc.* **259**, 374-377.
- Stein, A. A. (1970). Comparative toxicology of methoxychlor. In "Pesticides Symposia" (W. B. Diechmann, J. L. Radomski, and R. A. Penzance, eds.), Halos and Associates, Miami, Florida.
- Stein, A. A., Serrone, D. M., and Coulston, F. (1965). Safety evaluation of methoxychlor in human volunteers. *Toxicol. Appl. Pharmacol.* **7**, 499.
- Stein, K., Portig, J., and Koransky, W. (1977). Oxidative transformation of hexachlorocyclohexane in rats and with rat liver microsomes. *Naunyn-Schmiedberg's Arch. Pharmacol.* **298**, 115-128.
- Stein, K., Portig, J., Fuhrmann, H., Koransky, W., and Noack, G. (1980). Steric factors in the pharmacokinetics of lindane and  $\alpha$ -hexachlorocyclohexane in rats. *Xenobiotica* **10**, 65-77.
- Stein, V. B., Pittman, K. A., and Kennedy, M. W. (1976). Characterization of



- a mirex metabolite from monkeys. *Bull. Environ. Contam. Toxicol.* **15**, 140-146.
- Stein, W. J., and Hayes, W. J., Jr. (1964). Health survey of pest control operators. *Ind. Med. Surg.* **33**, 549-555.
- Stevens, H. (1970). Neurotoxicity of some common halogenated hydrocarbons. In "Laboratory Diagnosis of Diseases Caused by Toxic Agents" (F. W. Sunderman and F. W. Sunderman, Jr., eds.). Warren H. Green, St. Louis, Missouri.
- Stevens, J. T., Wagner, S. R., Zemaitis, M. A., and Greene, F. E. (1973). Effect of chronic dieldrin exposure on the hepatic microsomal mixed function oxidase system from male and female rats. *Toxicol. Appl. Pharmacol.* **25**, 484.
- Stevens, J. T., Oberholser, K. M., Wagner, S. R., and Greene, F. E. (1977). Content and activities of microsomal electron transport components during the development of dieldrin-inducer hypertrophic hypoactive endoplasmic transport. *Toxicol. Appl. Pharmacol.* **39**, 411-421.
- Stevenson, D. E., and Walker, A. I. T. (1969). Hepatic lesions produced in mice by dieldrin and other hepatic enzyme inducing components. *Eur. J. Toxicol.* **2**, 83-84.
- Stevenson, D. E., Thorpe, E., Hunt, P. F., and Walker, A. I. T. (1976). The toxic effects of dieldrin in rats: A reevaluation of data obtained in a two-year feeding study. *Toxicol. Appl. Pharmacol.* **36**, 247-254.
- Stickel, W. H., Stickel, L. F., and Spann, J. W. (1969). Tissue residues of dieldrin in relation to mortality in birds and mammals. In "Chemical Fallout" (M. W. Miller and G. G. Berg, eds.), pp. 174-204. Thomas, Springfield, Illinois.
- Stickel, W. H., Kaiser, T. E., and Reichel, W. L. (1979). Endrin versus 12-keto-endrin in birds and rodents. *ASTM Spec. Tech. Publ.* **STP 693**, 61-68.
- Stieglitz, R., Stobbe, H., and Schüttmann, W. (1967). Bone marrow damages after occupational exposure to the insecticide gammahexachlorocyclohexane (lindane). *Acta Haematol.* **38**, 337-350.
- Stieglitz, R., Stobbe, H., Schüttmann, W., Herrmann, H., and Schmidt, U. (1969). On the pathomechanism of panmyelophthises induced by the insecticide lindane. *Folia Haematol. (Leipzig)* **91**, 293-301 (in German).
- Stieglitz, R., Schüttmann, W., and Stobbe, H. (1971). Panmyelophthisis from occupational exposure to toxicants. *Dtsch. Gesundheitswes.* **26**, 910-916 (in German).
- Stijve, T., and Cardinale, E. (1972). On the residues associated with the use of technical grade BHC with special reference to the occurrence and determination of three pentachlorocyclohex-1-ene isomers. *Mitt. Geb. Lebensmittelunters. Hyg.* **63**, 142-152 (in German).
- Stoewsand, G. S., and Bourke, J. B. (1968). The influence of dietary protein on the resistance to dieldrin toxicity in the rat. *Ind. Med. Surg.* **37**, 526.
- Stoewsand, G. S., Broderick, E. J., and Bourke, J. B. (1970). Dietary protein and dieldrin toxicity. *Ind. Med. Surg.* **39**, 356-360.
- Stohlman, E. F., and Lillie, R. D. (1948). The effect of DDT on the blood sugar and of glucose administration on the acute and chronic poisoning of DDT in rabbits. *J. Pharmacol. Exp. Ther.* **93**, 351-361.
- Stohlman, E. F., Throp, W. T. S., and Smith, M. I. (1950). Toxic action of chlordane. *Arch. Ind. Hyg. Tidskr.* **36**, 77-81.
- Stören, G. (1955). A fatal case of poisoning by Jacutin (lindane) insecticide and moth-proofing agent. *Nord. Hyg. Tidskr.* **36**, 77-81 (in Swedish).
- Stoyanov, K. (1971). Biochemical alterations occurring in rats and sheep after acute poisoning with heptachlor. *Vet. Med. Nauki* **8**, 65-70 (in Russian).
- Stranger, J., and Kerridge, G. (1968). Multiple fractures of the dorsal part of the spine following chlordane poisoning. *Med. J. Aust.* **1**, 267-268.
- Strassman, S. C., and Kutz, F. W. (1977). Insecticide residues in human milk from Arkansas and Mississippi, 1973-1974. *Pestic. Monit. J.* **10**, 130-133.
- Street, J. C. (1964). DDT antagonism to dieldrin storage in adipose tissue of rats. *Science* **146**, 1580-1581.
- Street, J. C., and Blau, A. D. (1966). Insecticide interactions affecting residue accumulation in animal tissues. *Toxicol. Appl. Pharmacol.* **8**, 497-504.
- Street, J. C., and Chadwick, R. W. (1967). Stimulation of dieldrin metabolism by DDT. *Toxicol. Appl. Pharmacol.* **11**, 68-71.
- Street, J. C., Wang, M., and Blau, A. D. (1966a). Drug effects on dieldrin storage in rat tissue. *Bull. Environ. Contam. Toxicol.* **1**, 6-15.
- Street, J. C., Chadwick, R. W., Wang, M., and Phillips, R. L. (1966b). Insecticide interactions affecting residue storage in animal tissues. *J. Agric. Food Chem.* **14**, 545-549.
- Street, J. C., Mayer, F. L., and Wagstaff, D. J. (1969). Ecological significance of pesticide interactions. *Ind. Med. Surg.* **38**, 409-414.
- Stubblefield, W. A., and Dorough, H. W. (1979). Quantitative administration of insecticide vapors to rats. *Toxicol. Appl. Pharmacol.* **48**, A138.
- Study Group Ministry of Health and Welfare for Organochlorine Pesticide Residues in Mothers' Milk (1972). Studies on the analysis of pesticide residues in foods. VII. Organochlorine pesticide residues in mothers' milk. *J. Food Hyg. Soc. Jpn.* **13**, 422-437 (in Japanese).
- Stur, O., and Zweimüller, E. (1961). Diagnosis and therapy of acute gamma-hexachlorocyclohexane poisoning in infants. *Dtsch. Med. Wochenschr.* **86**, 1474-1476 (in German).
- Su, Y., and Zhou, Y. (1986). Histopathological effects of technical benzene hexachloride and lindane on rat liver and kidney. *Zhonghua Yufangyixue Zazhi* **20**, 356-358 (in Chinese).
- Subramony, S. H., Reddy, R. V., and Desai, D. (1982). Effects of chlordecone on nerve conductance in rats. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **41**, 1578.
- Sugaya, A. (1972). On the chronic cases of disturbance due to organochlorine pesticides. *J. Jpn. Assoc. Rural Med.* **21**, 362-363 (in Japanese).
- Sugaya, A., Hayashi, S., Meguro, Y., Minagawa, N., Sasaki, S., Suzuki, Y., and Watabe, K. (1976). Amount of organochlorine pesticide residues in human body. *J. Jpn. Soc. Rural Med.* **1-2**, 43-47 (in Japanese).
- Sugaya, T. et al. (1971). Organochlorine pesticide residues in human milk. *J. Jpn. Assoc. Rural Med.* **19**, 379-380 (in Japanese).
- Sund, R. R. C. V., Shreenivas, R., Singh, V., Perez, A. A., and Wolf, A. (1988). Disseminated intravascular coagulation in a case of fatal lindane poisoning. *Vet. Hum. Toxicol.* **30**, 132-134.
- Sundström, G. (1977). Metabolic hydroxylation of the aromatic rings of 1,1-dichloro-2,2-bis(4-chlorophenyl)ethylene (p,p'-DDE) by the rat. *J. Agric. Food Chem.* **25**, 18-21.
- Sundström, G., Jansson, B., and Jenson, S. (1975). Structure of phenolic metabolites of p,p'-DDE in rat, wild seal and guillemot. *Nature (London)* **255**, 627-628.
- Suñol, C., Tusell, J. M., Gelpi, E., and Rodríguez-Farré, E. (1988a). Convulsant effect of lindane and regional brain concentration of GABA and dopamine. *Toxicology* **49**, 247-252.
- Suñol, C., Tusell, J. M., Gelpi, E., and Rodríguez-Farré, E. (1988b). Regional concentrations of GABA, serotonin and noradrenaline in brain at onset of seizures induced by lindane (γ-hexachlorocyclohexane). *Neuropharmacology* **27**, 677-681.
- Sunöl, C., Tusell, J. M., Gelpi, E., and Rodríguez-Farré, E. (1989). GABA-ergic modulation of lindane (γ-hexachlorocyclohexane)-induced seizures. *Toxicol. Appl. Pharmacol.* **100**, 1-8.
- Suter, S., Trosko, J. E., Fouly, M. H., Lockwood, L. R., and Koestner, A. (1987). Dieldrin inhibition of gap junctional intercellular communication in rat glial cells as measured by the fluorescence photobleaching and scrape loading/dye transfer assays. *Fundam. Appl. Toxicol.* **9**, 785-794.
- Suvak, L. N. (1970). DDT in mothers' milk. *Zdravooch. Kosinev* **13**, 19-21 (in Russian).
- Suzaki, E., Inoue, B., Okimasu, E., Ogata, M., and Utsumi, K. (1988). Stimulative effect of chlordane on the various functions of guinea-pigs leukocyte. *Toxicol. Appl. Pharmacol.* **93**, 137-145.
- Suzuki, Y., Sugaya, H., and Sasaki, S. (1973). Results of 3 years' tracing investigation of organochlorine pesticide residues in humans. *J. Jpn. Assoc. Rural Med.* **22**, 276-277 (in Japanese).
- Suzuki, Y., Sugaya, H., and Sasaki, S. (1976). Organochlorine pesticide residues in humans 1975. *J. Jpn. Assoc. Rural Med.* **25**, 498-499 (in Japanese).
- Swanson, K., and Woolley, D. (1978). Neurotoxic effects of dieldrin. *Toxicol. Appl. Pharmacol.* **45**, 339.
- Swanson, K., and Woolley, D. E. (1982). Comparison of the neurotoxic effects of chlordecone and dieldrin in the rat. *Neurotoxicology* **3** (2), 81-102.
- Syllanco, C. Y. L. (1978). Some interactions affecting the mutagenicity potential of dipyrone, hexachlorophene, Thiodan and malathion. *Mutat. Res.* **53**, 272-272.
- Symanski, H. J. (1968). A case of fatal occupational aldrin intoxication. *Ind. Med. Surg.* **37**, 551.
- Syrowatka, T., Palut, D., Gorski, T., and Tulczynski, A. (1979). Residues of chloro-organic pesticides in adipose tissue of the population of Warsaw and environs. *Rocz. Panstw. Zakl. Hig.* **40**, 505-509 (in Polish).
- Syrowatka, T., Gorski, T., and Palut, D. (1981). Residues of organic chlorine pesticides in the blood of the population of Warsaw and environs in the fourth trimester of 1979. *Rocz. Panstw. Zakl. Hig.* 267-269 (in Polish).
- Szarmach, H., and Poniecka, H. (1973). Contact allergy in agriculture. *Przegl. Dermatol.* **60**, 479-484 (in Polish).
- Tabata, K., Mijata, T., and Saito, T. (1979). Water soluble metabolites of dicofol in mouse urine. *Appl. Entomol. Zool.* **14**, 490-493.
- Taira, M., Hashimoto, S., and Shimohira, I. (1972). Organochlorine pesticide residues in human breast milk. *Bull. Hyogo Prefect. Public Health Lab.* **7**, 19-23 (in Japanese).
- Takahashi, W., and Parks, L. H. (1982). Organochlorine pesticide residues in human tissues, Hawaii, 1968-1980. *Hawaii Med. J.* **41**, 250-251.
- Takamatsu, J., Kitazawa, A., Nakata, K., and Furukawa, K. (1981). Does mitotane reduce endogenous ACTH secretion? *N. Engl. J. Med.* **305**, 957.
- Takei, G. H., Kauahikaua, S. M., and Leong, G. H. (1983). Analyses of human milk samples collected in Hawaii for residues of organochlorine pesticides and polychlorobiphenyls. *Bull. Environ. Contam. Toxicol.* **30**, 606-613.
- Takeshita, T., and Inuyama, Y. (1970). Organochlorine residues in mothers' milk and blood. *Annu. Rep. Shimane Prefect. Inst. Public Health* **12**, 27-28 (in Japanese).
- Taliaferro, I., and Leone, L. (1957). Inhibitory effect of Perthane (2,2-bis[paraethylphenyl]-1,1-dichloroethane) on adrenocortical function in human subjects. *N. Engl. J. Med.* **257**, 855-860.
- Tanaka, K., Kurihara, N., and Nakajima, M. (1977). Pathways of chlorophenol formation in oxidative biodegradation of BHC. *Agric. Biol. Chem.* **41**, 723-725.
- Tanaka, K., Kurihara, N., and Nakajima, M. (1979a). Oxidative metabolism of tetrachlorocyclohexenes, pentachlorocyclohexenes, and hexachlorocyclohexenes with microsomes from rat liver and house fly abdomen. *Pestic. Biochem. Physiol.* **10**, 79-95.
- Tanaka, K., Kurihara, N., and Nakajima, M. (1979b). Oxidative metabolism of lindane and its isomers with microsomes from rat liver and house fly abdomen. *Pestic. Biochem. Physiol.* **10**, 96-103.
- Tanaka, R., Fujisawa, S., Nakai, K., and Minagawa, K. (1980). Distribution and biliary excretion of carbaryl, dieldrin and paraquat in rats: Effect of diets. *J. Toxicol. Sci.* **5**, 151-162.
- Tanaka, R., Fujisawa, S., and Nakai, K. (1981). Study on the absorption and protein binding of carbaryl, dieldrin and paraquat in rats fed on protein diet. *J. Toxicol. Sci.* **6**, 1-11.
- Tarján, R., and Kemény, T. (1969). Multigeneration studies on DDT in mice. *Food Cosmet. Toxicol.* **7**, 215-222.
- Tarmas, J., Stefanska-Sulik, E., and Pieczko-Kuduk, I. (1973). Morphologic changes in the central nervous system in guinea pigs under the influence of the pesticide Alvit 55. *Patol. Pol.* **24**, 295-302 (in Polish).
- Tashiro, S., and Matsumura, F. (1977). Metabolic routes of cis- and trans-chlordane in rats. *J. Agric. Food Chem.* **25**, 872-880.
- Tashiro, S., and Matsumura, F. (1978). Metabolism of trans-nonachlor and related chlordane components in rat and man. *Arch. Environ. Contam. Toxicol.* **7**, 113-127.
- Tashkhdzhayev, P. I., Nadjimutdinov, K. N., and Sharipova, N. M. (1973). Effect of hexachlorocyclohexane on the general morphology and ultrastructure of the liver. *Med. Zh. Uz.* **12**, 23-27 (in Russian).
- Taylor, J. R. (1982). Neurological manifestations in humans exposed to chlordecone and follow-up results. *Neurotoxicology* **3** (2), 9-16.
- Taylor, J. R. (1985). Neurological manifestations in humans exposed to chlordecone: Follow-up results. *Neurotoxicology* **6** (1), 231-236.
- Taylor, J. R., Selhorst, J. B., Houff, S. A., and Martinez, A. J. (1978). Chlordecone intoxication in man. I. Chemical observations. *Neurology* **28**, 626-630.
- Tegeris, A. S., Earl, F. L., Smalley, H. E., and Curtis, J. M. (1966). Methoxychlor toxicity. Comparative studies in the dog and swine. *Arch. Environ. Health* **13**, 776-787.
- Tegeris, A. S., VanderWeide, G. C., and Curtis, J. M. (1968). Progressive ultrastructural changes in the mucosal epithelium of the small intestine of beagle dogs fed methoxychlor. *Exp. Mol. Pathol.* **8**, 243-257.
- Telang, S., Tong, C., and Williams, G. M. (1982). Epigenetic membrane effects of a possible tumor promoter type on cultured liver cells by the non-genotoxic organochlorine pesticides chlordane and heptachlor. *Carcinogenesis (London)* **3**, 1175-1178.
- Telch, J., and Jarvis, A. (1982). Acute intoxication with lindane. *Can. Med. Assoc. J.* **126**, 662-663.
- Telford, H. S., and Guthrie, J. E. (1945). Transmission of the toxicity of DDT through the milk of white rats and goats. *Science* **102**, 647.
- Temple, T. E., Jones, D. J., Liddle, G. W., and Dexter, R. N. (1969). Treatment of Cushing's disease: Correction of hypercortisolism by o,p'-DDD without induction of aldosterone deficiency. *N. Engl. J. Med.* **281**, 801-805.
- Tennekes, H. A., Wright, A. S., Dix, K. M., and Koeman, J. H. (1981). Effects of dieldrin, diet, and bedding on enzyme function and tumor incidence in livers of male CF-1 mice. *Cancer Res.* **41**, 3615-3620.
- Tennekes, H. A., Edler, L., and Kunze, H. W. (1982). Dose-response analysis of the enhancement of liver tumor formation in CF-1 mice by dieldrin. *Carcinogenesis (London)* **3**, 941-945.
- Tennekes, H. A., van Ravenzwaay, B., and Kunz, H. W. (1985). Quantitative aspects of enhanced liver tumour formation in CF-1 mice by dieldrin. *Carcinogenesis (London)* **6**, 1457-1462.
- Terracini, B., Testa, M. C., Cabral, J. R., and Day, N. (1973). The effects of long-term feeding of DDT to BALB/c mice. *Int. J. Cancer* **11**, 747-764.
- Terziev, G., Dimitrova, N., and Rusev, P. (1974). Forensic medical and forensic chemical study of acute lethal poisonings with Thiodan. *Folia Med. (Plovdiv)* **16**, 325-329.
- Thamavit, W., Hiasa, Y., Ito, N., and Bhamarapravati, N. (1974). The inhibitory effects of α-benzene hexachloride on 3'-methyl-4-dimethylaminoazobenzene and DL-ethionine carcinogenesis in rats. *Cancer Res.* **34**, 337-340.
- Thielemann, H. (1979). Results from experimental studies on the question of the contamination of human milk by total DDT (DDT + DDE) in the urban district of Halle (Saale) in 1978. *Pharmazie* **34**, 665-666 (in German).
- Thielemann, H., Grahneis, H., and Haase, H. H. (1975). Studies concerning contamination of human milk with DDT within the city limits of Halle (Saale). *Z. Gesamte Hyg. Ihre Grenzgeb.* **21**, 685-687 (in German).
- Thompson, R. P. H., Pilcher, C. W. T., Robinson, J., Stathers, G. M., McLean, A. E. M., and Williams, R. (1969). Treatment of unconjugated jaundice with dicophane. *Lancet* **2**, 4-6.
- Thorne, B. M., Taylor, E., and Wallace, T. (1978). Mirex and behavior in the Long-Evans rat. *Bull. Environ. Contam. Toxicol.* **19**, 351-359.
- Thorpe, E., and Walker, A. I. T. (1973). The toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC and γ-BHC. *Food Cosmet. Toxicol.* **11**, 433-442.
- Tilson, H. A., and Gerhart, J. G. (1982). Time course and dose response assessment of chlordecone (C)-induced tremors in rats. **2**, 114.
- Tilson, H. A., and Mactutus, C. F. (1982). Chlordecone neurotoxicity: A brief overview. *Neurotoxicology* **3** (2), 1-8.
- Tilson, H. A., Byrd, N., and Riley, M. (1979). Neurobehavioral effects of exposing rats to Kepone via the diet. *Environ. Health Perspect.* **33**, 321.
- Tilson, H. A., Hong, J. S., and Mactutus, C. F. (1985). Effects of 5,5-diphenylhydantoin (phenytoin) on neurobehavioral toxicity of organochlorine insecticides and permethrin. *J. Pharmacol. Exp. Ther.* **233**, 285-289.
- Tilson, H. A., Hudson, P. M., and Hong, J. S. (1986). 5,5-Diphenylhydantoin antagonizes neurochemical and behaviour effects of p,p'-DDT but not of chlordecone. *J. Neurochem.* **47**, 1870-1878.
- Tilson, H. A., Shaw, S., and McLamb, R. L. (1987). The effects of lindane, DDT, and chlordecone avoidance responding and seizure activity. *Toxicol. Appl. Pharmacol.* **88**, 57-65.
- Timchalk, C., and Charles, A. K. (1986). Differential effects of carcinogens on hepatic cytosolic cyclic AMP-dependent protein kinase activity. *J. Am. Coll. Toxicol.* **5**, 267-273.



- Timchalk, C., Charles, A. K., and Abraham, R. (1985). Comparative changes in rat liver cytosolic proteins by mirex, diethylnitrosamine and dimethylnitrosamine exposure. *Proc. Soc. Exp. Biol. Med.* **180**, 214-223.
- Tinsley, I. J., and Lowry, R. R. (1972). An interaction of DDT in the metabolism of essential fatty acids. *Lipids* **7**, 182-185.
- To-Figueras, J., Rodamilans, M., Gómez, J., and Corbella, J. (1986). Hexachlorobenzene residues in the general population of Barcelona (Spain). *IARC Sci. Publ.* **77**, 147-148.
- Tokutsu, K., Koyama, T., and Yokoyama, T. (1970). Pesticide residue in mother's milk and plasma in Wakayama Prefecture. *Annu. Rep. Wakayama Prefect. Inst. Public Health* **19**, 59-62 (in Japanese).
- Tolot, F., Lenglet, J. P., Prost, G., and Bertholon, J. (1969). Polyneuritis due to lindane. *J. Med. Lyon* **50**, 747-748.
- Tomatis, L., and Turusov, V. (1975). Studies on the carcinogenicity of DDT. *Gann Monogr. Cancer Res.* **17**, 219-241.
- Tomatis, L., Turusov, V., Day, N., and Charles, R. T. (1972). The effect of long-term exposure to DDT on CF-1 mice. *Int. J. Cancer* **10**, 489-506.
- Tomatis, L., Partensky, C., and Montesano, R. (1973). The predictive value of mouse liver tumor induction in carcinogenicity testing—a literature survey. *Int. J. Cancer* **12**, 1-20.
- Tomatis, L., Turusov, V., Charles, R. T., and Boicchi, M. (1974a). Effect of long-term exposure to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane, and to the two chemicals combined on CF-1 mice. *J. Natl. Cancer Inst. (U.S.)* **52**, 883-891.
- Tomatis, L., Turusov, V., Charles, R. T., Boicchi, M., and Gati, F. (1974b). Liver tumors in CF-1 mice exposed for limited periods to technical DDT. *Z. Krebsforsch.* **82**, 25-35.
- Tomczak, S., Baumann, K., and Lehnert, G. (1981). Occupational exposure to hexachlorocyclohexane. IV. Sex hormone alterations in HCH-exposed workers. *Int. Arch. Occup. Environ. Health* **48**, 283-287.
- Tomii, S., Nagasaki, H., and Mega, Y. (1972). Studies on BHC as a carcinogen. *Jpn. J. Hyg.* **27**, 113 (in Japanese).
- Torda, C., and Wolff, H. G. (1949). Effect of convulsant and anticonvulsant agents on the activity of carbonic anhydrase. *J. Pharmacol. Exp. Ther.* **95**, 444-447.
- Törnblom, N. (1959). Administration of DDD (2,2-bis(parachlorophenyl)-1,1-dichloroethane) to diabetics with hyaline vascular changes and hyperpolysaccharidemia. *Acta. Med. Scand.* **16**, 23-27.
- Tosa, Y., Yasugi, N., Okada, N., Nagami, H., and Seki, R. (1971). A case of survival in endrin poisoning. *J. Jpn. Assoc. Rural Med.* **19**, 370-371 (in Japanese).
- Tottori Prefectural Hygiene Research Institute (1971). Tests and investigations on pesticide residues in mothers' milk and blood. *Rep. Tottori Prefect. Hyg. Res. Inst.* **11**, 19 (in Japanese).
- Toutou, Y., Bogdan, A., and Luton, J. P. (1978). Changes in corticosteroid synthesis of the human adrenal cortex *in vitro*, induced by treatment with o,p'-DDD for Cushing's syndrome: Evidence for the sites of action of the drug. *J. Steroid Biochem.* **9**, 1217-1224.
- Toutou, Y., Moolenaar, A. J., Bogdan, A., Auzéby, A., and Luton, J. P. (1985). o,p'-DDD (mitotane) treatment for Cushing's syndrome: Adrenal drug concentration and inhibition *in vitro* of steroid synthesis. *Eur. J. Clin. Pharmacol.* **29**, 483-487.
- Tovari, G. (1971). Acute poisoning by Thiodan in cattle. *Magy. Allatorv. Lapja* **26**, 343-345 (in Hungarian).
- Treinen, K. A., and Kulkarni, A. P. (1986). Human placental calcium ATPase: *In vitro* inhibition by DDT homologues. *Toxicol. Lett.* **30**, 223-229.
- Treon, J. F., and Cleveland, F. P. (1955). Toxicity of certain chlorinated hydrocarbon insecticides for laboratory animals with special reference to aldrin and dieldrin. *J. Agric. Food Chem.* **3**, 402-408.
- Treon, J. F., Cleveland, F. P., and Cappel, J. (1955). Toxicity of endrin for laboratory animals. *J. Agric. Food Chem.* **3**, 842-848.
- Trifonova, T. K., and Gladenko, I. N. (1980). Determination of gonado- and embryotoxicity of pesticides. *Veterinariya (Kiev)* **6**, 58-59 (in Russian).
- Trifonova, T. K., Gladenko, I. N., and Shulyak, V. D. (1970). Effect of gamma-BHC and Sevin on reproduction. *Veterinariya (Kiev)* **47**, 91-93 (in Russian).
- Triolo, A. J., and Coon, J. M. (1966a). Toxicologic interactions of chlorinated hydrocarbon and organophosphate insecticides. *J. Agric. Food Chem.* **14**, 549-555.
- Triolo, A. J., and Coon, J. M. (1966b). The protective effect of aldrin against the toxicity of organo-phosphate anticholinesterases. *J. Pharmacol. Exp. Ther.* **154**, 613-623.
- Trosko, J. E., Jones, C., and Chang, C. C. (1987). Inhibition of gap junction-mediated intercellular communication *in vitro* by aldrin, dieldrin, and toxaphene: A possible cellular mechanism for their tumor-promoting and neurotoxic effects. *Mol. Toxicol.* **1**, 83-93.
- Trottman, C. H., and Desai, D. (1979). Adenosine triphosphatase activities in brain, kidney and liver of mice treated with toxaphene. *J. Environ. Sci. Health, Part B* **14**, 393-404.
- Trottman, C. H., and Desai, D. (1980). Induction of rat hepatic microsomal enzymes by toxaphene pretreatment. *J. Environ. Sci. Health, Part B* **15**, 121-134.
- Trottman, C. H., and Desai, D. (1983). Effect of toxaphene on the binding of <sup>3</sup>H-labelled ouabain and dopamine to rat brain synaptosomes. *Toxicol. Lett.* **18**, 323-330.
- Trottman, C. H., Prasada Rao, K. S., Morrow, W., Uzodinman, J. E., and Desai, D. (1985). *In vitro* effects of toxaphene or mitochondrial calcium uptake in selected rat tissues. *Life Sci.* **36**, 427-433.
- Tryphonas, L., and Iverson, F. (1983). Sequential histopathic analysis of alpha-hexachlorocyclohexane-induced hepatic megalocytosis and adenoma formation in the HPBD mouse. *JNCI, J. Natl. Cancer Inst.* **71**, 1307-1318.
- Tseng, Y. C. L., and Menzer, R. E. (1974). Effect of hepatic enzyme inducers on the *in vivo* and *in vitro* metabolism of dicrotophos, dimethoate, and phosphamidon in mice. *Pestic. Biochem. Physiol.* **4**, 425-437.
- Tsushimoto, G., Trosko, J. E., Chang, C. C., and Matsumura, F. (1982). Inhibition of intercellular communication by chlordecone (Kepone) and mirex in Chinese hamster v 79 cells *in vitro*. *Toxicol. Appl. Pharmacol.* **64**, 550-556.
- Tsushimoto, G., Chang, C. C., Trosko, J. E., and Matsumura, F. (1983). Cytotoxic, mutagenic, and cell-cell communication inhibitory properties of DDT, lindane, and chlordane on Chinese hamster cells *in vitro*. *Arch. Environ. Contam. Toxicol.* **12**, 721-730.
- Tsutsui, J., Kato, T., and Nishikawa, T. (1974). Results of health survey on persons engaging in pesticide application in Suzuka area, Mie Prefecture. *J. Jpn. Assoc. Rural Med.* **23**, 518-521 (in Japanese).
- Tuinstra, L. G. M. T. (1971). Organochlorine insecticide residues in human milk in the Leiden region. *Ned. Melk Zuivelijdschr.* **25**, 24-32 (in Dutch).
- Tullner, W. W. (1961). Uterotrophic action of the insecticide methoxychlor. *Science* **133**, 647-648.
- Tullner, W. W., and Edgcomb, J. H. (1962). Cystic tubular nephropathy and decrease in testicular weight in rats following oral methoxychlor treatment. *J. Pharmacol. Exp. Ther.* **138**, 126-130.
- Turner, W. V., Khalifa, S., and Casida, J. E. (1975). Toxaphene toxicant A. Mixture of 2,2,5-endo,6-exo,8,8,9,10-octachlorobornane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane. *J. Agric. Food Chem.* **23**, 991-994.
- Turner, W. V., Engel, J. L., and Casida, J. E. (1977). Toxaphene components and related compounds: Preparation and toxicity of some hepta-, octa-, and nonachlorobornanes, hexa- and heptachlorobornenes, and a hexachlorobornadiene. *J. Agric. Food Chem.* **25**, 1394-1401.
- Tussell, J. M., Sunol, C., Gelpi, E., and Rodriguez-Farré, E. (1987). Relationship between lindane concentration in blood and brain and convulsant response in rats after oral or intraperitoneal administration. *Arch. Toxicol.* **60**, 432-437.
- Tyagi, S. R., Singh, Y., Srivastava, P. K., and Misra, U. K. (1984). Induction of hepatic mixed function oxidase system by endosulfan in rats. *Bull. Environ. Contam. Toxicol.* **32**, 550-556.
- Tzoneva-Maneva, M. T., Kalianova, F., and Georgieva, V. (1971). Influence of Diazinon and lindane on the mitotic activity and the caryotype of human lymphocytes, cultivated *in vitro*. *Bibl. Haematol. (Basel)* **38**, 344-347.
- Uchida, A., Ishige, T., Saito, M., and Oikawa, K. (1972). Results of the status of acute pesticide intoxications. *J. Jpn. Assoc. Rural Med.* **21**, 235-235 (in Japanese).
- Uchida, M., Kurihara, N., Fujita, T., and Nakajima, M. (1974). Inhibitory effects of BHC isomers on Na<sup>+</sup>-K<sup>+</sup>-ATPase, yeast growth, and nerve conduction. *Pestic. Biochem. Physiol.* **4**, 260-265.
- Ulland, B. M., Weisburger, E. K., and Weisburger, J. H. (1973). Chronic toxicity and carcinogenicity of industrial chemicals and pesticides. *Toxicol. Appl. Pharmacol.* **25**, 446.
- Ulland, B. M., Page, N. P., Squire, R. A., Weisburger, E. K., and Cypher, R. L. (1977). A carcinogenicity assay of mirex in Charles River CD rats. *J. Natl. Cancer Inst. (U.S.)* **58**, 133-140.
- Unger, M., and Olsen, J. (1980). Organochlorine compounds in the adipose tissue of diseased people with and without cancer. *Environ. Res.* **23**, 257-263.
- Unterman, H. W., and Sirghie, E. (1969). Storage of organochlorine in the human organism. *Igiene* **18**, 221-226 (in Romanian).
- Uphouse, L. (1986). Single injection with chlordecone reduces behavioral receptivity and fertility of adult rats. *Neurobehav. Toxicol. Teratol.* **8**, 121-126.
- Uphouse, L. (1987). Decreased rodent sexual receptivity after lindane. *Toxicol. Lett.* **39**, 7-14.
- Uphouse, L., and Eckols, K. (1986). Serotonin receptors in striatum after chlordecone treatment of adult female rats. *Neurotoxicology* **7** (1), 25-32.
- Uphouse, L., and Williams, J. (1989). Diestrous treatment with lindane disrupts the female rat reproductive cycle. *Toxicol. Lett.* **48**, 21-28.
- Uphouse, L., Mason, G., and Hunter, V. (1984). Persistent vaginal estrus and serum hormones after chlordecone (Kepone) treatment of adult female rats. *Toxicol. Appl. Pharmacol.* **72**, 177-186.
- Uphouse, L., Eckols, K., Sierra, V., Kolodziej, M., and Brown, H. (1986). Failure of chlordecone (Kepone) to induce behavioral estrus in adult ovariectomized female rats. *Neurotoxicology* **7** (1), 127-142.
- Urbanska-Bonenberg, L., and Langauer-Lewowicka, H. (1966). Polyorganic toxic action of dieldrin. *Med. Pr.* **17**, 336-339.
- U.S. Department of Agriculture (1945a). Release of February 13, 1945. Bureau of Entomology and Plant Quarantine, U.S. Dept. Agric., Washington, D.C.
- U.S. Department of Agriculture (1945b). "Outlook for Supplies of DDT Insecticides," Release of August 6, 1945. Bureau of Entomology and Plant Quarantine, U.S. Dept. Agric., Washington, D.C.
- U.S. Department of Agriculture (1949). "USDA Entomologists Recommend Substitute Insecticide for DDT to Control Insects on Dairy Cattle and in Dairy Barns," New Release, March 24, 1949. Agricultural Research Administration, U.S. Dept. Agric. Washington, D.C.
- U.S. Food and Drug Administration (1947). "Quarterly Report No. 3." U.S. Food Drug Admin., Washington, D.C.
- U.S. Environmental Protection Agency (USEPA) (1976). "Criteria Document for Toxaphene," EPA-440/9-76/014, Office of Water Planning and Standards, Washington, D.C.
- Usha Rani, M. V., Reddi, O. S., and Reddy, P. P. (1980). Mutagenicity studies involving aldrin, endosulfan, dimethoate, phosphamidon, carbaryl and Ceresan. *Bull. Environ. Contam. Toxicol.* **25**, 277-282.
- Utklev, H. E., and Westbye, C. (1971). Endosulfan poisoning. *Nor. Veterinaertidsskr.* **83**, 31 (in Swedish).
- Vaarama, A. (1947). The influence of DDT pesticides upon plant mitosis. *Hereditas* **33**, 191-219.
- Vainio, H. (1975). Stimulation of microsomal drug-metabolizing enzymes in rat liver by 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), p-nenolone-16 $\alpha$ -carbonitrile (PCN), and polychlorinated biphenyls (PCBs). *Environ. Qual. Saf.* **3**, 486-490.
- Vainio, H., and Parkki, M. G. (1976). Enhancement of microsomal monooxygenase, epoxide hydride and UDP-glucuronyltransferase by aldrin, dieldrin and isosafrole administrations in rat liver. *Toxicology* **5**, 279-286.
- van Asperen, K. (1954). Interaction of the isomers of benzene hexachloride in mice. *Arch. Int. Pharmacodyn. Ther.* **99**, 368-377.
- Vanat, S. V., and Vanat, I. M. (1971). Contribution to the toxic-allergic reaction induced by DDT. *Klin. Med. (Moscow)* **49**, 126-127 (in Russian).
- Van den Bercken, J., and Narahashi, T. (1974). Effects of aldrin-transdiol—a metabolite of the insecticides dieldrin—on nerve membrane. *Eur. J. Pharmacol.* **27**, 255-258.
- van der Linden, T. (1912). Decomposition of benzene hexachloride in tri-chlorobenzene. *Ber. Dtsch. Chem. Ges.* **45**, 231-247 (in German).
- Van Gelder, G. A., and Cunningham, W. L. (1975). The effect of low-level dieldrin exposure on the EEG and learning ability of the squirrel monkey. *Toxicol. Appl. Pharmacol.* **33**, 142.
- Van Gelder, G. A., and Smith, R. M. (1973). Delayed acquisition of a successive reversal behavioral task in dieldrin-dosed squirrel monkeys. *Toxicol. Appl. Pharmacol.* **25**, 485.
- van Raalte, H. G. S. (1977). Human experience with dieldrin in perspective. *Ecotoxicol. Environ. Saf.* **1**, 203-210.
- van Ravenswaay, B., and Kunz, W. (1988). Quantitative aspects of accelerated nuclear polyploidization and tumour formation in dieldrin treated CF-1 mouse liver. *Br. J. Cancer* **58**, 52-56.
- van Ravenswaay, B., Tennekens, H., Stoehr, M., and Kunz, W. (1987). The kinetics of nuclear polyploidization and tumor formation in livers of CF-1 mice exposed to dieldrin. *Carcinogenesis (London)* **8**, 265-269.
- van Ravenswaay, B., Toussaint, H. J. M., and Schmitt, R. L. (1988). Dieldrin-induced changes in isozyme composition in the livers of CF-1 mice. *Int. J. Cancer* **41**, 305-308.
- Van Velsen, F. L., Danse, L. H. J. C., Van Leluwen, F. X. R., Dormans, J. A. M. A., and Van Logten, M. J. (1986). The subchronic oral toxicity of the  $\beta$ -isomer of hexachlorocyclohexane in rats. *Fundam. Appl. Toxicol.* **6**, 697-712.
- Vanyurykhina, L. T. (1972). Effect of adrenal cortex function inhibitor clodithane (o,p'-DDD) on blood serum proteins. *Fiziol. Zh. (Kiev, 1955-1977)* **18**, 591-595 (in Russian).
- Vas'Kovskaja, L. F. (1969). Accumulation of certain chloroorganic insecticides in the bodies of experimental animals and humans. *Kiev, Vnigintox* **7**, 503-796 (in Russian).
- Vas'Kovskaja, L. F., and Komarova, L. I. (1963). Quoted by Y.S. Kagan et al., *Residue Rev.* **27**, 43-79 (in Russian).
- Vaz, A., Pereira, R. S., and Malheiro, D. M. (1945). Calcium in prevention and treatment of experimental DDT poisoning. *Science* **101**, 434-436.
- Velbinger, H. H. (1947a). Question of "DDT"—toxicity for humans. *Dtsch. Gesundheitswes.* **2**, 355-358 (in German).
- Velbinger, H. H. (1947b). Contribution to the toxicology of "DDT"—active substances of dichlorodiphenyltrichloromethylmethane. *Pharmazie* **2**, 268-274 (in German).
- Velbinger, H. H. (1949). Different effects of the new insecticides "DDT," Gammexan and E605. *Pharmazie* **4**, 165-176 (in German).
- Veltkamp, J. J., Stevens, P., von der Plas, M., and Loeliger, E. A. (1970). Production site of bleeding factor (acquired morbus von Willebrand). *Thromb. Diath. Haemorrh.* **23**, 412.
- Verdon, T. A., Bruton, J., Herman, R. H., and Beisel, W. R. (1962). Clinical and chemical response of functioning adrenal cortical carcinoma to ortho,para-DDD. *Metab., Clin. Exp.* **11**, 226-234.
- Versteeg, J. P. J., and Jager, K. W. (1973). Long-term exposure to the insecticide aldrin, dieldrin, endrin, and Telodrin. *Br. J. Ind. Med.* **30**, 201-202.
- Vila, M. C., Aldonatti, C., and San Martin de Viale, L. C. (1986). Evaluation of porphyrinogenic effect of lindane in rats. *Acta Physiol. Latinoam.* **36**, 69-76.
- Villeneuve, D. C., Yagminas, A. P., Marino, I. A., Chu, I., and Reynolds, L. M. (1977). Effects of food deprivation in rats previously exposed to mirex. *Bull. Environ. Contam. Toxicol.* **18**, 278-284.
- Villeneuve, D. C., Ritter, L., Felsky, G., Norström, R. J., Marion, I. A., Valli, V. E., Chu, I., and Becking, G. C. (1979a). Short-term toxicity of photomirex in the rat. *Toxicol. Appl. Pharmacol.* **47**, 105-114.
- Villeneuve, D. C., Valli, V. E., Chu, I., Secours, V., Ritter, L., and Becking, G. C. (1979b). 90-Day toxicity of photomirex in the male rat. *Toxicology* **12**, 235-250.
- Violante, F. S., Gennari, P., Raffi, G. B., Coltelli, E., Lev, D., Minak, G., and Tiraferri, S. (1986). Study of DDT blood level in a group of workers exposed to pesticides. *Arch. Environ. Health* **41**, 117-119.
- Virgo, B. B., and Bellward, G. D. (1973a). Effect of dietary dieldrin on the liver and drug metabolism in the SWV mouse. *Proc. Can. Fed. Biol. Soc.* **16**, 69.



- Virgo, B. B., and Bellward, G. D. (1973b). Effect of dieldrin on mouse reproduction. *Proc. Can. Fed. Biol. Soc.* **16**, 103.
- Virgo, B. B., and Bellward, G. D. (1975a). Effects of dietary dieldrin on the liver and drug metabolism in the female Swiss-Vancouver mouse. *Can. J. Physiol. Pharmacol.* **53**, 903-911.
- Virgo, B. B., and Bellward, G. D. (1975b). Effects of dietary dieldrin on reproduction in the Swiss-Vancouver (SMV) mouse. *Environ. Physiol. Biochem.* **5**, 440-450.
- Virgo, B. B., and Bellward, G. D. (1977). Effects of dietary dieldrin on offspring viability, maternal behavior, and milk production in the mouse. *Res. Commun. Chem. Pathol. Pharmacol.* **17**, 399-409.
- Vogel, E. (1972). Mutagenicity studies with DDT and its metabolites DDE, DDD, DDOM and DDA in *Drosophila melanogaster*. *Mutat. Res.* **16**, 157-164.
- Vohland, H. W., and Koransky, W. (1972). Effect of  $\alpha$ -hexachlorocyclohexane on metabolism and excretion of pentetrazol (Cardiazol) in the rat. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **273**, 99-108.
- Vohland, H. W., Koransky, W., and Zufelde, H. (1972). Effect of  $\alpha$ -hexachlorocyclohexane on the convulsive activity of pentetrazol (Cardiazol) in the rat. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **275**, 289-298.
- Vohland, H. W., Portig, J., and Stein, K. (1981). Neuropharmacological effects of isomers of hexachlorocyclohexane. 1. Protection against pentylenetetrazol-induced convulsions. *Toxicol. Appl. Pharmacol.* **57**, 425-438.
- von Oettingen, W. F., and Sharpless, N. E. (1946). The toxicity and toxic manifestations of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) as influenced by chemical changes in the molecule. A contribution to the relation between chemical constitution and toxicological action. *J. Pharmacol. Exp. Ther.* **88**, 400-413.
- Vu, N., Chepko, G., and Zelenka, P. (1983). Decreased turnover of phosphatidylinositol accompanies *in vitro* differentiation of embryonic chicken lens epithelial cells into lens fibres. *Biochim. Biophys. Acta* **750**, 105-111.
- Wagner, S. R., and Greene, F. E. (1974). Effects of acute and chronic dieldrin exposure on brain biogenic amines of male and female rats. *Toxicol. Appl. Pharmacol.* **29**, 119.
- Wagner, S. R., and Greene, F. E. (1978). Dieldrin-induced alterations in biogenic amine content of rat brain. *Toxicol. Appl. Pharmacol.* **43**, 45-55.
- Wagstaff, D. J., and Street, J. C. (1971a). Ascorbic acid deficiency and induction of hepatic microsomal hydroxylative enzymes by organochlorine pesticides. *Toxicol. Appl. Pharmacol.* **19**, 10-19.
- Wagstaff, D. J., and Street, J. C. (1971b). Antagonism of DDT storage in guinea pigs by dietary dieldrin. *Bull. Environ. Contam. Toxicol.* **6**, 273-278.
- Wakita, M., Hoshino, S., Morimoto, K., Yamada, K., Miyata, K., and Tsubota, H. (1972). BHC (1,2,3,4,5,6-hexachlorocyclohexane) residues in sheep. *Jpn. J. Zootech. Sci.* **43**, 620-624 (in Japanese).
- Wali, R. K., Singh, R., Dudeja, P. K., and Mahmood, A. (1982). Effect of a single oral dose of endosulfan on intestinal uptake of nutrients and on brush-border enzymes in rats. *Toxicol. Lett.* **12**, 7-12.
- Walker, A. I. T., Stevenson, D. E., Robinson, J., Thorpe, E., and Roberts, M. (1969). The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. *Toxicol. Appl. Pharmacol.* **15**, 345-373.
- Walker, A. I. T., Thorpe, E., Robinson, J., and Baldwin, M. K. (1971). Toxicity studies on the photo-isomerisation product of dieldrin. *Meded. Fac. Landbouwwet. Rijksuniv. Gent* **36**, 398-409.
- Walker, A. I. T., Thorpe, E., and Stevenson, D. E. (1973). The toxicology of dieldrin (HEOD). I. Long-term oral toxicity studies in mice. *Food Cosmet. Toxicol.* **11**, 415-432.
- Walker, C. H., Timms, C. W., Wolf, C. R., and Oesch, F. (1986). The hydration of sterically hindered epoxides by epoxide hydrolase of the rat and rabbit. *Biochem. Pharmacol.* **35**, 499-503.
- Walker, J. F., and Phillips, D. E. (1987). An electron microscopic study of endrin induced alterations in unmyelinated fibers of mouse sciatic nerve. *Neurotoxicology* **8** (1), 55-64.
- Wallace, Z. E., Silverstein, J. N., Villalodid, L. S., and Weisenfeld, S. (1961). Cushing's syndrome due to adrenocortical hyperplasia. *N. Engl. J. Med.* **265**, 1088-1093.
- Walsh, G. M., and Fink, G. B. (1970). Temporal aspects of acute endrin toxicity in mice. *Proc. West. Pharmacol. Soc.* **13**, 81-83.
- Walton, M. S., Bastone, V. B., and Baron, R. L. (1971). Subchronic toxicity of photodieldrin, a photodecomposition product of dieldrin. *Toxicol. Appl. Pharmacol.* **20**, 82-88.
- Wang, C. M., and Matsumura, F. (1969). Dieldrin effect on the ion transport activities in liver tissues. *Bull. Environ. Contam. Toxicol.* **41**, 144-151.
- Wang, H. H., and MacMahon, B. (1979a). Mortality of pesticide applicators. *J. Occup. Med.* **221**, 741-744.
- Wang, H. H., and MacMahon, B. (1979b). Mortality of workers employed in the manufacture of chlordane and heptachlor. *J. Occup. Med.* **21**, 745-748.
- Wang, X. Q., Gao, P. Y., Lin, Y. Z., and Chen, C. M. (1988). Studies on hexachlorocyclohexane and DDT contents in human cerumen and their relationship to cancer mortality. *Biomed. Environ. Sci.* **1**, 138-151.
- Ware, G. W., and Good, E. E. (1967). Effects of insecticides on reproduction in the laboratory mouse. II. Mirex, Telodrin and DDT. *Toxicol. Appl. Pharmacol.* **10**, 54-61.
- Wariishi, M., Suzuki, Y., and Nishiyama, K. (1986). Chlordane residues in normal human blood. *Bull. Environ. Contam. Toxicol.* **36**, 635-643.
- Wärngård, L., Flodström, S., Ljungquist, S., and Ahlberg, U. G. (1985). Inhibition of metabolic cooperation in Chinese hamster lung fibroblast cells (V79) in culture by various DDT-analogs. *Arch. Environ. Contam. Toxicol.* **14**, 541-546.
- Wärngård, L., Flodström, S., Ljungquist, S., and Ahlberg, U. G. (1987). Interaction between quercetin, TPA and DDT in the V79 metabolic cooperation assay. *Carcinogenesis (London)* **8**, 1201-1205.
- Wärngård, L., Fransson, R., Flodström, S., Drakenberg, T.-B., and Ahlberg, U. G. (1988). Calmodulin involvement in TPA and DDT induced inhibition of intercellular communication. *Chem.-Biol. Interact.* **65**, 41-49.
- Wärngård, L., Hemming, H. J., Flodström, S., Duddy, S. K., and Kass, G. E. N. (1989). Mechanistic studies on the DDT-induced inhibition of intercellular communication. *Carcinogenesis (London)* **10**, 471-476.
- Warnick, S. L., and Carter, J. E. (1972). Some findings in a study of workers occupationally exposed to pesticides. *Arch. Environ. Health* **25**, 265-270.
- Warraki, S. (1963). Respiratory hazards of chlorinated camphene. *Arch. Environ. Health* **7**, 253-256.
- Warren, R. J., Kirkpatrick, R. L., and Young, R. W. (1978). Barbiturate-induced sleeping times, liver weights, and reproduction of cottontail rabbits after mirex ingestion. *Bull. Environ. Contamin. Toxicol.* **19**, 223-228.
- Wasicky, R., and Unti, O. (1944). Dichloro-diphenyl trichloroethane (DDT) does not control culicine larvae. *Arch. Hig.* **9**, 87-102.
- Wasicky, R., and Unti, O. (1945). Dichloro-diphenyl-trichloroethane (DDT). Recent investigations on its properties and uses. *Arch. Hig.* **10**, 49-64.
- Wassermann, D., Wassermann, M., and Lazarovici, S. (1970). Effects of adrenalectomy on the storage of organochlorine insecticides. *Bull. Environ. Contam. Toxicol.* **5**, 373-378.
- Wassermann, M., Iliescu, S., Mandric, G., and Horvath, P. (1960). Toxic hazards during DDT- and BHC-spraying of forests against *Lymantria monacha*. *AMA Arch. Ind. Health* **21**, 503-508.
- Wassermann, M., Pebdefunda, G., Merling, M., Mihail, G., Sandulescu, G., and Vancea, G. (1961). Research on environmental conditions and on occupational pathology of *Anopheles* eradicators. Chronic poisoning by hexachlorocyclohexane (HCH). II. Clinical modifications caused by the action of HCH on *Anopheles* eradicators. *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **22**, 308-317 (in French).
- Wassermann, M., Mihail, G., Vancea, G., Mandric, G., Iliescu, S., Railleau, D. B., Losubas, I. S., and Nestor, L. (1962). Research on environmental conditions and on the occupational pathology of *Anopheles* eradicators. Chronic poisoning by hexachlorocyclohexane (HCH). Correlation between clinical, chronaximetric and biochemical disorders. *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **23**, 18-31 (in French).
- Wassermann, M., Gon, M., Wassermann, D., and Zellermyer, L. (1965). DDT and DDE in the body fat of people in Israel. *Arch. Environ. Health* **11**, 375-379.
- Wassermann, M., Wassermann, D., Zellermyer, L., and Gon, M. (1967). Pesticides in people. Storage of DDT in the people of Israel. *Pestic. Monit. J.* **1**, 14-20.
- Wassermann, M., Curnow, D. H., Forte, P. N., and Groner, Y. (1968a). Storage of organochlorine pesticides in the body fat of people in Western Australia. *Ind. Med. Surg.* **37**, 295-300.
- Wassermann, M., Sofuluwe, G. I., Wassermann, D., Groner, Y., and Lazarovitch, S. (1968b). Storage of organochlorine insecticides in the body fat of people in Nigeria. In "Proceedings of the Lagos International Seminar on Occupational Health for Developing Countries, Lagos, Nigeria, April 1-6."
- Wassermann, M., Wassermann, D., and Ivriani, I. (1970a). Organochlorine insecticides in the plasma of occupationally exposed workers. In "Pesticides Symposia" (W. B. Diechmann, J. L. Radomski, and R. A. Penzler, eds.), Halos and Associates, Miami, Florida.
- Wassermann, M., Wassermann, D., Lazarovici, S., Coetzee, A. M., and Tomatis, L. (1970b). Present state of the storage of the organochlorine insecticides in the general population of South Africa. *S. Afr. Med. J.* **44**, 646-648.
- Wassermann, M., Wassermann, D., Kedar, E., and Djavaherian, M. (1971). Immunological and detoxication interactions in *p,p'*-DDT fed rabbits. *Bull. Environ. Contam. Toxicol.* **6**, 426-534.
- Wassermann, M., Wassermann, D., Kedar, E., Djavaherian, M., and Cucos, S. (1972a). Effects of dieldrin and gamma BHC on serum proteins and PBI. *Bull. Environ. Contam. Toxicol.* **8**, 177-185.
- Wassermann, M., Rogoff, M. G., Tomatis, L., Day, N. E., Wassermann, D., Djavaherian, M., and Guttel, C. (1972b). Storage of organochlorine insecticides in the adipose tissue of people of Kenya. *Ann. Soc. Belge Med. Trop.* **52**, 509-514.
- Wassermann, M., Nogueira, D. P., Tomatis, L., Athie, E., Wassermann, D., Djavaherian, M., and Guttel, C. (1972c). Storage of organochlorine insecticides in people of São Paulo, Brazil. *Ind. Med. Surg.* **41**, 22-25.
- Wassermann, M., Trishnanada, M., Tomatis, L., Day, N. E., Wassermann, D., Rungpitarangsi, V., Chiamsakol, V., and Cucos, S. (1972d). Storage of organochlorine insecticides in the adipose tissue of people in Thailand. *Southeast Asian J. Trop. Med. Public Health* **3**, 280-285.
- Wassermann, M., Sofuluwe, G. O., Tomatis, L., Day, N. E., Wassermann, D., and Lazarovici, S. (1972e). Storage of organochlorine insecticides in people in Nigeria. *Environ. Physiol. Biochem.* **2**, 59-67.
- Wassermann, M., Tomatis, L., Wassermann, D., Day, N. E., and Djavaherian, M. (1974a). Storage of organochlorine insecticides in adipose tissue of Ugandans. *Bull. Environ. Contam. Toxicol.* **12**, 501-508.
- Wassermann, M., Tomatis, L., Wassermann, D., Day, N. E., Groner, Y., Lazarovici, S., and Rosenfeld, D. (1974b). Epidemiology of organochlorine insecticides in the adipose tissue of Israelis. *Pestic. Monit. J.* **8**, 1-7.
- Watari, N. (1973). Ultrastructural alterations of the mouse liver after the prolonged administration of BHC. *J. Clin. Electron Microsc.* **5**, 1410-1420, 1449-1456.
- Watari, N., and Torizawa, K. (1972). Ultrastructural alterations of the mouse pancreas after prolonged administration of BHC. *J. Electron Microsc.* **21**, 334 (in Japanese).
- Watson, M., Benson, W. W., and Gabica, J. (1970). Serum organochlorine pesticide levels in people in southern Idaho. *Pestic. Monit. J.* **4**, 47-50.
- Weatherholz, W. M., and Webb, R. E. (1971). Influence of dietary protein on the activity of microsomal epoxidase in the growing rat. *J. Nutr.* **101**, 9-12.
- Weatherholz, W. M., Campbell, T. C., and Webb, R. E. (1969). Effect of dietary protein levels on toxicity and metabolism of heptachlor. *J. Nutr.* **98**, 90-94.
- Webb, R. E., and Miranda, C. L. (1973). Effect of the quality of dietary protein on heptachlor toxicity. *Food, Cosmet. Toxicol.* **11**, 63-67.
- Webb, R. E., Randolph, W. C., and Horsfall, F. (1972). Hepatic benzpyrene hydrolase activity in endrin susceptible and resistant pine mice. *Life Sci.* **11**, (Part 2), 477-483.
- Webb, R. E., Hartgrove, R. W., Randoolph, W. C., Petrella, V. J., and Horsfall, F., Jr. (1973). Toxicity studies in endrin-susceptible and resistant strains of pine mice. *Toxicol. Appl. Pharmacol.* **25**, 42-47.
- Weeks, D. E. (1967). Endrin food-poisoning. A report on four outbreaks caused by two separate shipments of endrin contaminated flour. *Bull. W.H.O.* **37**, 499-512.
- Weithe, M. (1966). Chlorinated insecticides in the body fat of people in Denmark. *Ugeskr. Laeg.* **128**, 881-882.
- Weinig, E., Machbert, G., and Zink, P. (1966). Proof of dieldrin in dieldrin poisoning. *Arch. Toxikol.* **22**, 115-124.
- Weisenberg, E., Arad, I., Grauer, F., and Sahn, Z. (1985). Polychlorinated biphenyls and organochlorine insecticides in human milk in Israel. *Arch. Environ. Contam. Toxicol.* **14**, 517-521.
- Weisenfeld, S., and Goldner, M. G. (1962). Treatment of advanced malignancy and Cushing's syndrome with DDD. *Cancer Chemother. Rep.* **16**, 335-339.
- Welch, H. (1948). Tests of the toxicity to sheep and cattle of certain of the newer insecticides. *J. Econ. Entomol.* **41**, 36-39.
- Welch, R. M., Levin, W., and Conney, A. H. (1969). Estrogenic action of DDT and its analogs. *Toxicol. Appl. Pharmacol.* **14**, 358-367.
- Welch, R. M., Levin, W., Kuntzman, R., Jacobson, M., and Conney, A. H. (1971). Effect of halogenated hydrocarbon insecticides on the metabolism and uterotrophic action of estrogens in rats and mice. *Toxicol. Appl. Pharmacol.* **19**, 234-246.
- Wells, W. L., and Milborn, H. T. (1983). Suicide attempt by toxaphene ingestion: A case report. *J. Miss. State Med. Assoc.* **24**, 329-330.
- Welsh, J. H., and Gordon, H. T. (1946). The mode of action of DDT. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **5**, 1.
- West, I. (1964). Pesticides as contaminants. *Arch. Environ. Health* **9**, 626-631.
- West, I. (1967). Lindane and hematologic reactions. *Arch. Environ. Health* **15**, 97-101.
- West, I., and Milby, T. H. (1965). Public health problems arising from the use of pesticides. *Residue Rev.* **11**, 140-159.
- West, P. R., Chaudhary, S. K., Branton, G. R., and Mitchell, R. H. (1982). High-performance liquid chromatographic analysis of impurities and degradation products of methoxychlor. *J. Assoc. Off. Anal. Chem.* **65**, 1457-1470.
- Westoo, G., and Noren, K. (1978). Organochlorine contaminants in human milk, Stockholm, 1967-1977. *Ambio* **7**, 62-64.
- Westoo, G., Noren, K., and Andersson, M. (1970). Levels of organochlorine pesticides and polychlorinated biphenyls in margarine, vegetable oils, and some foods of animal origin on the Swedish market in 1967-69. *Var. Foeda* **22**, 9-31.
- White, W. C., and Sweeney, T. R. (1945). The metabolism of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT). I. A metabolite from rabbit urine di-(*p*-chlorophenyl)-acetic acid; its isolation, identification, and synthesis. *Public Health Rep.* **60**, 66-71.
- Whitehead, C. C., Downing, A. G., and Pettigrew, R. J. (1972). The effects of lindane on laying hens. *Br. Poult. Sci.* **13**, 293-299.
- Wickström, K., Pyysalo, H., and Siimes, M. A. (1983). Levels of chlordane, hexachlorobenzene, PCB and DDT compounds in Finnish milk in 1982. *Bull. Environ. Contam. Toxicol.* **31**, 251-256.
- Wiener, M., Pittman, K. A., and Stein, V. (1976). Mirex kinetics in rhesus monkey. I. Disposition and excretion. *Drug Metab. Dispos.* **4**, 281-287.
- Wigglesworth, V. B. (1945). A case of DDT poisoning in man. *Br. Med. J.* **1**, 517.
- Wilcox, A. R. (1967). "USPH Investigation—DDT Health Effects," Inter-office correspondence to M. V. Anthony. Stauffer Chemical Co.
- Wildemaue, C., Lontie, J.-F., Schoofs, L., and van Larebeke, N. (1983). The mutagenicity in procaryocytes of insecticides, acaricides, and nematocides. *Residue Rev.* **89**, 129-178.
- Willhite, C., and Sharma, R. P. (1978). Acute dieldrin exposure in relation to brain monoamine oxidase activity and concentration of brain serotonin and 5-hydroxyindoleacetic acid. *Toxicol. Lett.* **2**, 71-75.
- Williams, C. H., and Casterline, J. L. (1970). Effects on toxicity and on enzyme activity of the interactions between aldrin, chlordane, piperonyl butoxide and Banol in rats. *Proc. Soc. Exp. Biol. Med.* **135**, 46-50.
- Williams, D. J., and Rabin, B. R. (1971). Disruption by carcinogens of the hormone dependent association of membranes with polysomes. *Nature (London)* **232**, 102-105.
- Williams, D. T., LeBel, G. L., and Jenkins, E. (1984). A comparison of



- organochlorine residues in human adipose tissue autopsy samples from two Ontario municipalities. *J. Toxicol. Environ. Health* **13**, 19-29.
- Williams, F. M., Woodhouse, K. W., Middleton, D., Wright, P., James, O., and Rawlins, M. D. (1982). Aldrin epoxidation in small samples of human liver. *Biochem. Pharmacol.* **31**, 3701-3703.
- Williams, G. M. (1980). Classification of genotoxic and epigenetic hepatocarcinogens using liver culture assays. *Ann. N.Y. Acad. Sci.* **349**, 273-282.
- Williams, G. M., and Numoto, S. (1984). Promotion of mouse liver neoplasms by the organochlorine pesticides chlordane and heptachlor in comparison to dichlorodiphenyltrichloroethane. *Carcinogenesis (London)* **5**, 1689-1696.
- Williams, G. M., Telang, S., and Tong, C. (1981). Inhibition of intercellular communication between liver cells by the liver tumor promoter 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane. *Cancer Lett.* **11**, 339-344.
- Williams, J., Eckols, K., Stewart, G., and Uphouse, L. (1988). Proestrous effects of chlordane on the serotonin system. *Neurotoxicology* **9**, 597-610.
- Williams, J., Eckols, K., and Uphouse, L. (1989). Estradiol and chlordane interactions with the estradiol receptor. *Toxicol. Appl. Pharmacol.* **98**, 413-421.
- Williams, J. D., and Yarbrough, J. D. (1983). The relationship between mirex-induced liver enlargement and the adrenal glands. *Pestic. Biochem. Physiol.* **19**, 15-22.
- Wilson, D. J., Locker, D. J., Ritzen, C. A., Watson, J. T., and Schaffner, W. (1973). DDT concentrations in human milk. *Am. J. Dis. Child.* **125**, 814-817.
- Wilson, D., and Yarbrough, J. D. (1988). Autoradiographic analysis of hepatocytes in mirex-induced adaptive liver growth. *Am. J. Physiol.* **255**, G132-G139.
- Wilson, H. F., Allen, N. N., Bohstedt, G., Bethell, J., and Lardy, H. A. (1946). Feeding experiments with DDT-treated pea vine silage with special reference to dairy cows, sheep, and laboratory animals. *J. Econ. Entomol.* **39**, 801-806.
- Wilson, J. S. (1959). Lindane poisoning in a family. *Med. J. Aust.* **2**, 684.
- Wilson, K. A., and Cook, R. M. (1970). Metabolism of xenobiotics in ruminants: Use of activated carbon as an antidote for pesticide poisoning in ruminants. *J. Agric. Food Chem.* **18**, 437-440.
- Winteringham, F. P. W., and Barnes, J. M. (1955). Comparative response of insects and mammals to certain halogenated hydrocarbons used as insecticides. *Physiol. Rev.* **35**, 701-739.
- Winthrop, G. J., and Felice, J. F. (1957). A clinical toxicological study of spraymen of a chlorinated hydrocarbon insecticide. *Bol. Of. Sanit. Panam.* **43**, 512-517.
- Wit, S. L. (1964). Aspects of toxicology and chemical analysis of insecticide residues. *Voeding* **25**, 609-628.
- Wolburg, I. (1973). The use of electroencephalography in industrial toxicology. *Act. Nerv. Super.* **15**, 226-235 (in German).
- Wolf, C. R. (1986). Cytochrome P-450s: Polymorphic multigene families involved in carcinogen activation. *Trends Genet.* **2**, 209-214.
- Wolfe, H. R., and Armstrong, J. F. (1971). Exposure of formulating plant workers to DDT. *Arch. Environ. Health* **23**, 169-176.
- Wolfe, H. R., Walker, K. C., Elliott, J. W., and Durham, W. F. (1959). Evaluation of the health hazards involved in house spraying with DDT. *Bull. W.H.O.* **20**, 1-14.
- Wolfe, J. L., Esher, R. J., Robinson, K. M., and Yarbrough, J. D. (1979). Lethal and reproductive effects of dietary mirex and DDT on old-field mice, *Peromyscus polionotus*. *Bull. Environ. Contam. Toxicol.* **21**, 397-402.
- Wolff, G. L., and Suber, R. L. (1986). Hepatic glutathione S-transferase activity in mice. Effects of A<sup>y</sup>/-genotype, obesity, lindane treatment, and sex. *Proc. Soc. Exp. Biol. Med.* **181**, 535-541.
- Wolff, G. L., Roberts, D. W., Morrissey, R. L., Greenman, D. L., Allen, R. R., Campbell, W. L., Bergman, H., Nesnow, S., and Frith, C. H. (1987). Tumorigenic responses to lindane in mice: Potentiation by a dominant mutation. *Carcinogenesis (London)* **8**, 1889-1897.
- Wolff, T., and Guengerich, F. P. (1987). Rat liver cytochrome P-450 isozymes as catalysts of aldrin epoxidation in reconstituted monooxygenase systems and microsomes. *Biochem. Pharmacol.* **36**, 2581-2588.
- Wolff, T., Greim, H., Huang, M., Miwa, G., and Lu, A. Y. H. (1980). Aldrin epoxidation catalysed by purified rat-liver cytochromes P-450 and P-448. *Eur. J. Biochem.* **111**, 545-551.
- Wong, O., Brocker, W., Davis, H. V., and Nagle, G. S. (1984). Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB and DDT. *Br. J. Ind. Med.* **41**, 15-24.
- Woodard, B. T., Ferguson, B. B., and Wilson, D. J. (1976). DDT levels in milk of rural indigent blacks. *Am. J. Dis. Child.* **130**, 400-403.
- Woodard, G., and Hagan, E. C. (1947). Toxicological studies on the isomers and mixtures of isomers of benzene hexachloride. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **6**, 386.
- Woodard, G., Ofner, R. R., and Montgomery, C. M. (1945). Accumulation of DDT in body fat and its appearance in the milk of dogs. *Science* **102**, 177-178.
- Woodliff, H. J., Connor, P. M., and Scopa, J. (1966a). Aplastic anaemia associated with insecticides. *Med. J. Aust.* **1**, 628-629.
- Woodliff, H. J., Connor, P. M., and Scopa, J. (1966b). Aplastic anaemia associated with insecticides (letter). *Med. J. Aust.* **1**, 915-916.
- Wooldridge, W. E. (1948). The gamma isomer of hexachlorocyclohexane in the treatment of scabies. *J. Invest. Dermatol.* **10-11**, 363-366.
- Woolley, D. E. (1982). Neurotoxicity of DDT and possible mechanisms of action. In "Mechanisms of Action of Neurotoxic Substances" (K. Prasad and A. Vemadakis, eds.), pp. 95-141. Raven Press, New York.
- Woolley, D. E. (1985). Application of neurophysiological techniques to toxicological problems: An overview. *Fundam. Appl. Toxicol.* **5**, 1-8.
- Woolley, D., Zimmer, L., Hasson, Z., and Swanson, K. (1984). Do some insecticides and heavy metals produce long-term potentiation in the limbic system? In "Cellular and Molecular Toxicology" (T. Narahashi, ed.), pp. 45-69. Raven Press, New York.
- Woolley, D., Zimmer, L., Dodge, D., and Swanson, K. (1985). Effects of lindane-type insecticides in mammals: Unsolved problems. *Neurotoxicology* **6** (2), 165-192.
- Worden, A. N. (1969). Toxicity of Telodrin. *Toxicol. Appl. Pharmacol.* **14**, 556-573.
- World Health Organization (WHO) (1958). "Note by Secretariat on Aldrin Poisoning in Kenya," Inf. Circ. Toxic. Pestic. Man, No. 1, p. 3. World Health Organ., Geneva.
- World Health Organization (WHO) (1959). "Report of Fatal Case of Aldrin Poisoning in an African Child (personal communication)," Inf. Circ. Toxic. Pestic. Man, No. 3, p. 1. World Health Organ., Geneva.
- World Health Organization (WHO) (1971). The place of DDT in operations against malaria and other vector-borne diseases. In "Official Records of the World Health Organization, No. 190," Executive Board Forty-Seventh Session. Part II. Report on the Proposed Program and Budget Estimates for 1972. Appendix 14, pp. 176-182. World Health Organ., Geneva.
- World Health Organization (WHO) (1973). "Safe Use of Pesticides. Twentieth Report of the WHO Expert Committee on Insecticides," Tech. Rep. Ser. No. 513. World Health Organ., Geneva.
- World Health Organization (WHO) (1974). Some organochlorine pesticides. *IARC Monogr. Eval. Carcinog. Risk Chem. Man* **5**.
- World Health Organization (WHO) (1977). Outbreak of food poisoning of chemical origin. *Wkly. Epidemiol. Rec.* **52**, 217.
- World Health Organization (WHO) (1979). "Environmental Health Criteria 9. DDT and Its Derivatives." United Nations Environment Programme and the World Health Organization, Geneva.
- Wrenn, T. R., Weyant, J. R., Fries, G. F., and Bitman, J. (1971a). Effect of several dietary levels of o,p'-DDT on reproduction and lactation in the rat. *Bull. Environ. Contam. Toxicol.* **6**, 471-479.
- Wrenn, T. R., Randall, J., Weyant, R., Fries, G. F., and Bitman, J. (1971b). Influence of dietary o,p'-DDT on reproduction and lactation of ewes. *J. Anim. Sci.* **33**, 1288-1292.
- Wright, A. S., Potter, D., Wooder, M. F., Donninger, C., and Greenland, R. D. (1972). The effects of dieldrin on the subcellular structure and function of mammalian liver cells. *Food Cosmet. Toxicol.* **10**, 311-322.
- Wright, A. S., Akintonwa, D. A. A., and Wooder, M. F. (1977). Studies on the interactions of dieldrin with mammalian liver cells at the subcellular level. *Ecotoxicol. Environ. Saf.* **1**, 7-16.
- Wright, A. S., Donninger, C., Greenland, R. D., Stemmer, K. L., and Zvon, M. R. (1978). The effect of prolonged ingestion of dieldrin on the livers of male rhesus monkeys. *Ecotoxicol. Environ. Saf.* **1**, 477-502.
- Wyllie, J., Gabica, J., and Benson, W. W. (1972). Comparative organochlorine pesticide residues in serum and biopsied lipid tissue: A survey of 200 persons in southern Idaho—1970. *Pestic. Monit. J.* **6**, 84-88.
- Yadav, A. S., Vashishat, R. K., and Kakar, S. N. (1982). Testing of endosulfan and fenitrothion for genotoxicity in *Saccharomyces cerevisiae*. *Mutat. Res.* **105**, 403-407.
- Yakushiji, T., Watanabe, I., Kuwabara, K., Yoshida, S., Koyana, K., and Kunita, N. (1979). Levels of polychlorinated biphenyls (PCBs) and organochlorine pesticides in human milk and blood collected in Osaka Prefecture from 1972 to 1977. *Int. Arch. Occup. Environ. Health* **43**, 1-15.
- Yamada, T., and Sakamoto, Y. (1973). Results of survey of pesticide residues in mother's milk and soil. *Annu. Rep. Hiroshima Prefect. Inst. Prevent. Environ. Pollut.* **3**, 57-58 (in Japanese).
- Yamagishi, T., Takeba, K., Fujimoto, C., Morimoto, K., and Haruta, M. (1972a). On the organochlorine pesticide residues in mother's body and her fetus' body. *Rep. Tokyo Public Health Stud.* **50**, 44-45 (in Japanese).
- Yamagishi, T., Fujimoto, C., Takeba, K., Morimoto, K., and Haruta, M. (1972b). Effects of  $\beta$ -BHC on the mouse fetus. *Rep. Tokyo Public Health Stud.* **50**, 46-47 (in Japanese).
- Yamagishi, T., Takeba, K., Fujimoto, C., Morimoto, K., and Haruta, M. (1972c). On the effects of  $\beta$ -BHC on the fetus of mouse. IV. *J. Clin. Nutr.* **41**, 599-604.
- Yamaguchi, I., Matsumura, F., and Kadous, A. A. (1979). Inhibition of synaptic ATPases by heptachlorepoide in rat brain. *Pestic. Biochem. Physiol.* **11**, 285-293.
- Yamaguchi, I., Matsumura, F., and Kadous, A. A. (1980). Heptachlor epoxide: Effects on calcium-mediated transmitter release from brain synaptosomes in rat. *Biochem. Pharmacol.* **29**, 1815-1823.
- Yamaguchi, M., Tanaka, S., Kawashima, K., Nakaura, S., and Tananaka, A. (1987). Effects of heptachlor on fetal developments of rats. *Eisei Shikensho Hokoku* **105**, 33-36 (in Japanese).
- Yamaguchi, S., Kaku, S., Kuwahara, Y., and Yamada, A. (1976). Epidemiological findings and evaluation of the amount of organochlorine pesticides in human blood plasma in Japan. (1976). *Arch. Environ. Contam. Toxicol.* **3**, 448-460.
- Yamamoto, K., Konoshita, K., and Uchihiro, T. (1973). A case of secondary erythroderma possibly due to BHC. *Case Hist.* **6**, 61-62.
- Yamamoto, T., Egashira, T., Yamanaka, Y., Takerni, Y., and Kuroiwa, Y. (1983). Initial metabolism of gamma-hexachlorocyclohexane ( $\gamma$ -HCH) by rat liver microsomes. *J. Pharmacobiodyn.* **6**, 721-728.
- Yarbrough, J. D., Chambers, J. E., Grimley, J. M., Alley, E. G., Fang, M. M., Morrow, J. T., Ward, B. C., and Conroy, J. D. (1981). Comparative study of 8-monohydromirex and mirex toxicity in male rats. *Toxicol. Appl. Pharmacol.* **58**, 105-117.
- Yarbrough, J. D., Grimley, J. M., Karl, P. I., Chambers, J. E., Case, R. S., and Alley, E. G. (1983). Tissue disposition, metabolism, and excretion of cis- and trans-5,10-dihydrogen mirex. *Drug Metab. Dispos.* **11**, 611-614.
- Yarbrough, J. D., Brown, L. D., and Grimley, J. O. (1984). Mirex-induced adaptive liver growth: A corticosterone-mediated response. *Cell Tissue Kinet.* **17**, 465-473.
- Yarbrough, J. D., Grimley, J. M., and Alley, E. G. (1986a). Induction of the hepatic cytochrome P-450 dependent monooxygenase system by cis- and trans-5,10-dihydrogen mirex. *Toxicol. Lett.* **32**, 65-71.
- Yarbrough, J. D., Grimley, J. M., and Karl, P. I. (1986b). Relationship of ornithine decarboxylase and thymidine kinase to mirex-induced liver growth. *Am. J. Physiol.* **251**, G859-G865.
- Yoder, J. M., Watson, M., and Benson, W. W. (1973). Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. *Mutat. Res.* **21**, 335-340.
- Yoshimoto, H., Kaneko, T., Horiuchi, S., Yonemaru, H., and Ideda, Y. (1972). Long-term toxicity of beta-BHC. *Folia Pharmacol. Jpn.* **68**, 243 (in Japanese).
- Young, R. A., and Mehendale, H. M. (1986). Effect of endrin and endrin derivatives on hepatobiliary function and carbon tetrachloride-induced hepatotoxicity in male and female rats. *Food Chem. Toxicol.* **34**, 863-868.
- Zaidi, S. S. A. (1987). Possible role of rat liver NADPH cytochrome P-450 reductase in the detoxication of DDT to DDD. *Bull. Environ. Contam. Toxicol.* **39**, 327-333.
- Zakirov, U. B., Volokhvianskiy, Y. A., and Kadyrov, U. Z. (1973). Effect of small doses of hexachlorocyclohexane after a lengthy period of administration on the activity of small intestine enzymes. *Med. Zh. Uzb.* **12**, 28-31 (in Russian).
- Zarkevich, N. F., Brusilovskiy, Y. S., and Orlov, N. S. (1973). Evaluation of the functional state of the kidneys using radioisotope renography in nephropathies of chemical etiology. *Gig. Tr. Prof. Zabol.* **17**, 28-32 (in Russian).
- Zavon, M. R., and Hamman, R. E. (1961). Human experience with dieldrin in malaria control programs. *Am. J. Public Health* **51**, 1026-1034.
- Zavon, M. R., Hine, C. H., and Parker, K. D. (1965). Chlorinated hydrocarbon insecticides in human body fat in the United States. *JAMA, J. Am. Med. Assoc.* **193**, 837-839.
- Zeidler, O. (1874). Compounds of chloral with bromo- and chlorobenzene. *Ber. Dtsch. Chem. Ges.* **7**, 1180-1181 (in German).
- Zein-el-Dine, K. (1946). The insecticide DDT. *J. Egypt. Med. Assoc.* **29**, 38-54.
- Zeller, F. J., and Hauser, H. (1974). Induction of polyploidy in cereal grains in lindane-based seed dressings. *Experientia* **30**, 345-348.
- Zemaitis, M. A., Oberholzer, K. M., and Greene, E. E. (1976). Effects of acute and chronic dieldrin administration on liver and plasma esterases of the rat. *Toxicol. Appl. Pharmacol.* **37**, 29-37.
- Zhong-Xiang, L., Kavanagh, T., Trosko, J. E., and Chang, C. C. (1986). Inhibition of gap junctional intercellular communication in human teratocarcinoma cells by organochlorine pesticides. *Toxicol. Appl. Pharmacol.* **83**, 10-19.
- Zhu, J., Feng, Z., and Chen, J. (1986). Studies on the distribution and fate of [ $\gamma$ -<sup>3</sup>H]hexachlorocyclohexane in rats. *Pestic. Biochem. Physiol.* **25**, 414-419.
- Ziem, G. (1982). Aplastic anaemia after methoxychlor exposure. *Lancet* **2**, 1349.
- Zimmerli, B., and Marek, B. (1973). The pesticide burden of the Swiss population (analyses of prepared meals, human fat, human serum, cigarettes, and cosmetics). *Mitt. Geb. Lebensmittelunters. Hyg.* **64**, 459-479 (in German).
- Zimmerman, B., Bloch, H. S., Williams, W. L., Hitchcock, C. R., and Hoeischer, B. (1956). Effects of DDT (1,1-dichloro-2,2-bis(p-chlorophenyl)-ethane) on human adrenal. Attempt to use adrenal destructive agent in treatment of disseminated mammary and prostatic cancer. *Cancer (Philadelphia)* **9**, 940-948.
- Zolotnikova, G. P., and Somov, B. A. (1978). On the role of pesticides in the occurrence of occupational dermatitis in workers of hothouses. *Vestn. Dermatol. Venerol.* **4**, 76-79 (in Russian).
- Zumoff, B. (1979). The hypouricemic effect of o,p-DDD. *Am. J. Med. Sci.* **278**, 145-147.